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Copper: Ambient Water Quality Criteria

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Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for copper. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgement. It does not reflect consi....

KEYWORDS: *Water quality, *Toxicology, *Copper, *Toxic substances, *Water pollution effects(Humans).

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CRITERION DOCUMENT

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CRITERIA

Aquatic Life

For copper the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(0.65\cdot\ln(\text{hardness})-1.94}$" as a 24-hour average (see the figure "24-hour average copper concentration vs. Hardness") and the concentration should not exceed "$e^{(0.88\cdot(\text{hardness}) - 1.03)}$" (see the figure "maximum copper concentration vs. hardness") at any time.

For copper the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.79 ug/l as a 24-hour average and the concentration should not exceed 18 ug/l at any time.

Human Health

To prevent the adverse organoleptic effects of copper in water, a criterion of 1 mg/l has been established.

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Introduction

Copper is a soft heavy metal, atomic number 29, with an atomic weight of 63.54, a melting point of 1,083°C, a boiling point of 2,595°C, and a density in elemental form at 20° of 8.9 g/cc (Stecher, 1968). Elemental copper is readily attacked by organic and mineral acids that contain an oxidizing agent and is slowly soluble in ammonia water. The halogens attack copper slowly at room temperature to yield the corresponding copper halide. Oxides and sulfides are also reactive with copper.

Copper has two oxidation states; Cu I (cuprous) and Cu II (cupric). Cuprous copper is unstable in aerated water over the pH range of most natural waters (6 to 8) and will oxidize to the cupric state (Garrels and Christ, 1965). Bivalent copper chloride, nitrate, and sulfate are highly soluble in water whereas basic copper carbonate, cupric hydroxide, oxide, and sulfide will precipitate out of solution or form colloidal suspensions in the presence of excess cupric ion. Cupric ions are also adsorbed by clays, sediments, and organic particulates and form complexes with several inorganic and organic compounds (Riemer and Toth, 1969; Stiff, 1971). Due to the complex interactions of copper with numerous other chemical species normally found in natural waters, the amounts of the various copper compounds and complexes that actually exist in solution will depend on the pH, temperature, alkalinity, and the concentrations of bicarbonate, sulfide, and organic ligands. Based on equilibrium constants, Stumm and Morgan (1970) calculated copper solubility in a carbonate bearing water. They found that cupric ion (Cu^{2+}) would be the dominant copper species up to pH 6 and from pH 6 to 9.3 the aqueous copper carbonate complex ($CuCO_3$ aq.) would dominate. The presence of organic ligands such as humic acids, fulvic acids, amino acids, cyanide, certain polypeptides, and detergents would alter this equilibrium (Stiff, 1971).

Zirino and Yamamoto (1972) developed a model to predict the distribution of copper species in seawater. Mixed ligand complexes and organic chelates were not considered in the model. They predicted that the distribution of copper species in seawater would vary significantly with pH and that $Cu(OH)_2$, $CuCO_3$ and Cu^{2+} would be the dominant species over the entire ambient pH range. The levels of $Cu(OH)_2$ increase from about 18 percent of the total copper at pH 7 to 90 percent at pH 8.6. $CuCO_3$ drops from about 30 percent at pH 7 to less than 0.1 percent at pH 8.6 Field and laboratory studies by Thomas and Grill (1977) indicate that copper adsorbed to sediments and particulates in freshwater may be released as soluble copper when it comes in contact with seawater in estuarine environments.

Copper is ubiquitous in the rocks and minerals of the earth's crust. In nature copper occurs usually as sulfides and oxides and occasionally as metallic copper. Weathering and solution of these natural copper minerals results in background levels of copper in natural surface waters at concentrations generally well below 20 µg/l. Higher concentrations of copper are usually from anthropogenic sources.

These sources include corrosion of brass and copper pipe by acidic waters, industrial effluents and fallout, sewage treatment plant effluents, and the use of copper compounds as aquatic algicides. Potential industrial copper pollution sources number in the tens of thousands in the United States. However, the major industrial sources include the smelting and refining industries, copper wire mills, coal burning industries, and iron and steel producing industries. Copper may enter natural waters either directly from these sources or by atmospheric fallout of air pollutants produced by these industries. Precipitation to atmospheric fallout may be a significant source of copper to the aquatic environment in industrial and mining areas.

The levels of copper able to remain in solution are directly dependent on water chemistry. Generally, ionic copper is more soluble in low pH, low alkalinity waters and less soluble in high pH, high alkalinity waters. Copper is an essential trace element for humans as well as for many other life forms. In humans most of this copper requirement is obtained from food. Although copper poisoning in humans is rare, ingestion of milligram quantities of ionic copper (usually from acidic waters or foods exposed to copper) can cause acute symptoms of nausea, vomiting and diarrhea. Many aquatic organisms are more sensitive than man to copper and significant changes in the aquatic community may occur at copper concentrations significantly lower than those hazardous to human health. Copper occurs at higher concentrations in freshwater than in seawater and is more toxic to aquatic life in soft acidic waters than in hard alkaline waters.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Copper, which occurs in natural waters primarily as the divalent cupric ion (free and complexed forms), is a minor nutrient for both plants and animals at low concentrations but is acutely toxic to aquatic life at concentrations only slightly higher. Usual concentrations of 1-10 µg/l (total copper) are reported for a majority of surface waters in the United States. Concentrations in the vicinity of municipal and industrial outfalls, particularly smelting, refining, or metal plating industries, may exceed 500 µg/l.

The cupric ion is highly reactive and forms moderate to strong complexes and precipitates with many inorganic and organic constitutents of natural waters, e.g. carbonate, phosphate, amino-acids, and humates, and is readily absorbed on surfaces of suspended solids. The proportion of total copper present as the free cupric ion is generally low, and may be less than one percent in eutrophic waters where complexation predominates. Fortunately, the various copper complexes and precipitates appear to be largely non-toxic and tend to mask or remove toxicity attributable to total copper (Andrew, 1976). This fact greatly complicates the interpretation and application of available toxicity data, since the proportion of free cupric ion present is highly variable and is difficult to measure except under ideal laboratory conditions. Few toxicity data have been generated using measurements of other than total or dissolved copper. As evidenced by the criteria derived herein, concentrations required for survival, growth and reproduction of the more sensitive aquatic species are at or below ambient total concentrations in some surface waters of the United States. This results from a majority of the tests having been conducted with oligotrophic waters.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

Seasonally and locally, toxicity may be mitigated by the presence of naturally occurring chelating, complexing, and precipitating agents. Removal from the water column may be rapid due to normal growth of the more resistant species and settling of solids. The various forms of copper are in dynamic equilibrium and any change in chemical conditions, e.g. pH, could rapidly alter the proportion of the various forms present, and therefore, toxicity.

Since increasing calcium hardness and associated carbonate alkalinity are both known to reduce copper toxicity, expression of the criteria as a function of water hardness (see Figures labeled "24-hour average copper concentration vs. hardness" and "maximum copper concentration vs. hardness"), allows adjustment of the criteria based on total copper concentration for these water quality effects. This results in a much better fit with the available toxicity data. That is, the criteria are higher at high hardness to reflect calcium antagonism and carbonate complexation in the receiving waters.

The following data on the effects of copper on aquatic biota (Tables 1-7) have been summarized from the literature from 1950-1978. Efforts to obtain residue data, or effects data on algae and other plants were not exhaustive, since earlier reviews indicated these effects to be of minor importance relative to toxicity to fish and invertebrate species.

Acute Toxicity

Acute toxicity tests with copper have been conducted on a total of 29 fish species (Table 1), with nearly 250 values available for comparison. Most of these tests have been conducted with four salmonid species, fathead and bluntnose minnows, and bluegills.

Unadjusted values range from a low of 10 µg/l for chinook salmon in soft water to 10,000 µg/l for bluegills tested in hard water. The majority of tests conducted since about 1970 have been flow-through tests with measurements of both total and dissolved copper. Where available, LC50 values based on dissolved copper have been included and notated in the tables.

Following the Guidelines, an exponential equation describing the relationship of toxicity to hardness for each species was fit by least squares regression of the natural logarithms of the LC50 values and hardness.

There were sufficient data available for five species to show correlation of acute toxicity and water hardness. These were the chinook salmon, cutthroat and rainbow trout, fathead minnows, and bluegills. The slope of the regression equations ranged from 0.72 for chinnok salmon to 0.84 for bluegills, with a mean of 0.79. The close agreement of the slopes and the highly significant ($p = 0.01$) regressions in each case reflect the quality of the toxicological data available, the steepness of the slopes, and the similarity in response of the species tested.

In the absence of contradictory data, it will be assumed that the hardness relationship holds for all aquatic species. Adjustments for hardness effects on toxicity were made for all species by fitting the mean slope (0.79) through the geometric mean toxicity value and hardness for each species. Logarithmic intercepts were then used as a measure of relative species sensitivity to copper. Chinook salmon is the most sensitive fish species. Rainbow trout and the other salmonids are somewhat less sensitive. Fathead minnows and several other cyprinids are approximately 3-11 times more resistant to copper than the salmonids. Bluntnose minnows however, are nearly as sensitive as the salmonids. Bluegills and other centrarchids are approximately 20-110 times more resistant than salmonids. These results indicate that the 1,000 fold-range in LC50 values observed in Table 1 is largely a function of water quality, and that the actual range of sensitivity is more narrow.

Following the Guidelines, the mean intercept, adjusted by the species sensitivity factor, for all 29 fish species is 1.12. Since results of flow-through tests with measured concentrations for both rainbow trout and chinook salmon are lower than this, the data for chinook salmon are used to derive the final fish acute equation. Thus the Final Fish Acute Value is $e^{(0.72 \cdot \ln(\text{hardness}) + 0.83)}$.

The overall variation observed in acute toxicity values for invertebrate species (Table 2) is nearly the same as that for fish, with adjusted values ranging from 4.2 µg/l for *Daphnia hyalina* to 10,200 µg/l for eggs of snails (*Amnicola* sp.) and 9,100 µg/l for adult stoneflies (*Acroneuria lycorias*). However, hardness effects are much more difficult to determine with the invertebrate data, since few species have been tested over a range of water quality (particularly hardness). Sufficient data were available however, to show a weak dependence on hardness ($r = 0.39$) for copper toxicity to *Daphnia magna*, and a somewhat better relationship ($r = 0.51$, $p = 0.05$) for *Daphnia pulicaria*. The slopes (0.75 and 1.03) were similar to those for fish. The calculated mean intercept for the 26 invertebrate species that have been tested is 2.01, which indicates that the invertebrate species are acutely more sensitive than fish.

After using the calculated intercepts as a measure of relative species sensitivities, the range of sensitivity is much greater than for fish. This wider range may be the result of a greater taxonomic diversity than exists for fish.

Daphnia hyalina, the most sensitive species (intercept = -2.25), is approximately 70 times more sensitive to copper than indicated by the mean sensitivity. At least eight or nine invertebrate species are more sensitive than chinook salmon. The most resistant adult insects, however, have not been tested in hardnesses higher than 40-50 g/l. Even with adjustment of the data for hardness effects, the overall range of sensitivities is approximately 3,000-fold.

Using the Guidelines, the adjusted mean intercept is -1.03, which is adequate to protect all species except possibly Daphnia hyalina. Only a single LC50 value, run under static conditions with unmeasured copper concentrations, is available for this species. The adjusted mean intercept thus appears adequate for invertebrate species. The Final Invertebrate Acute Value is $e^{(0.88 \cdot \ln (\text{hardness}) - 1.03)}$. Since this value is lower than that for fish, it becomes the Final Acute Value.

Chronic Toxicity

The fish chronic values (Table 3) range from 1.9 μg/l for embryo-larval tests with brook trout in soft water to 75.4 μg/l for a life cycle test with fathead minnows in very hard water. Only for fathead minnows are there enough data to indicate the relationship of chronic toxicity to hardness. The slope (0.65) is similar to that (0.77) for acute toxicity values for the same species (Table 1). The correlation ($r = 0.82$) is nonsignificant primarily because of the small number of chronic test values available. Using the fathead minnow slope and adjusting for hardness effects as for the acute values, the relative sensitivity of the fish appears to be consistent with the acute results. That is, salmonids are the most sensitive group, blue gills much more resistant, and the minnows intermediate. For chronic tests, northern pike was the most resistant species. There are, however, no LC50 values for this species for comparison.

1-1

The mean logarithmic intercept for the 11 species tested is -0.042. Comparing this intercept with the mean intercept for acute values for fish (2.48), indicates that fish are approximately 12 times more sensitive when exposed chronically to copper, than acutely. This is equivalent to an application factor of 0.08, which agrees closely with the mean application factor (0.067) derived from the seven values available (Table 3).

The adjusted mean intercept (-1.94) using the species sensitivity factor (6.7) from the Guidelines is adequate to protect brook trout and bluntnose minnows, the most sensitive species. The Final Fish Chronic Value is thus $e^{(0.65 \cdot \ln \text{(hardness)} - 1.94)}$.

Seven invertebrate species (four of which were daphnids) have been tested for chronic effects of copper (Table 4). Chronic values spanned the range of 6.1 to 49 µg/l. Three other species were more sensitive than daphnids at equivalent hardnesses.

No hardness relationship could be derived for any invertebrate species. Assuming a similar hardness relationship as with fish chronic values, the slope (0.65) results in a mean intercept for the seven invertebrate species of 0.21. This is not significantly different from that for fish. The adjusted mean intercept (-1.42) is also slightly above that for fish.

The derived equation for fish chronic values: $e^{(0.65 \cdot \ln \text{(hardness)} - 1.94)}$ is therefore used as the Final Chronic Value.

Plant Effects

Copper has been widely used in the past as an algicide and herbicide for nuisance aquatic plants. Although copper is known as an inhibitor of photosynthesis and plant growth, toxicity data on individual species (Table 5) are not numerous. The relationship of toxicity to water chemistry and the importance of the culture medium has only recently been recognized (Gachter, et al. 1973).

Copper concentrations from 1 to 8,000 µg/l have been shown to inhibit growth of various plant species. Several of the values are near or below the chronic values for fish and invertebrate species. Since the values indicated cause lag in growth or inhibit photosynthesis, they should be considered important ecological effects of copper. Calculations using the equation for Final Fish Chronic Value indicate that even the most sensitive algal species would be adequately protected in waters with a hardness greater than 20 µg/l. In extremely soft water, some growth reduction of Chlorella sp. might be expected to occur at the Final Chronic Value. This single result does not seem to warrant lowering the criteria, however.

Residues

Bioconcentration factors (Table 6) ranged from 203 for stoneflies (P. californica) to 2,000 for the alga (Chlorella regularis). Since copper is a required element for animal nutrition, the importance of copper residues has never been established and few tests have been run for the purpose of determining bioconcentration factors.

CRITERION FORMULATION

Freshwater-Aquatic Life

Summary of Available Data

All concentrations herein are expressed in terms of copper.

Final Fish Acute Value = $e^{(0.72 \cdot \ln(\text{hardness}) + 0.83)}$

Final Invertebrate Acute Value = $e^{(0.88 \cdot \ln(\text{hardness}) - 1.03}$

Final Acute Value = $e^{(0.88 \cdot \ln(\text{hardness}) - 1.03)}$

Final Fish Chronic Value = $e^{(0.65 \cdot \ln(\text{hardness}) - 1.94)}$

Final Invertebrate Chronic Value = $e^{(0.65 \cdot \ln(\text{hardness}) - 1.42)}$

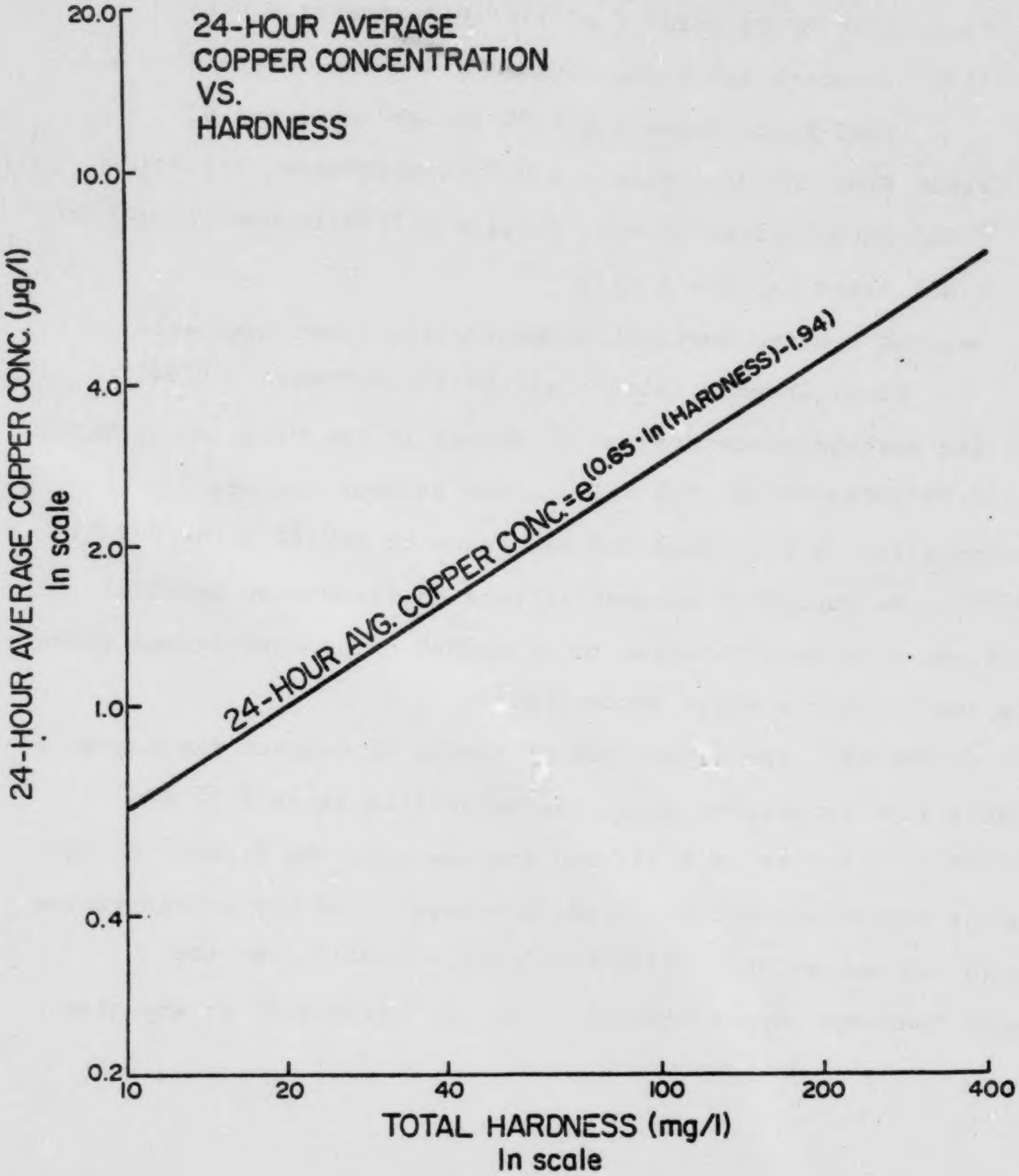
Final Plant Value = 1 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = $e^{(0.65 \cdot \ln(\text{hardness}) - 1.94)}$

The maximum concentration of copper is the Final Acute Value of $e^{(0.88 \cdot \ln(\text{hardness}) - 1.03)}$ and the 24-hour average concentration is the Final Chronic Value of $e^{(0.65 \cdot \ln(\text{hardness}) - 1.94)}$. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For copper the criterion to protect freshwater aquatic life as derived using the Guidelines is "$e^{(0.65 \cdot \ln(\text{hardness}) - 1.94)}$" as a 24-hour average (see the figure "24-hour average copper concentration vs. hardness") and the concentration should not exceed "$e^{(0.88 \cdot \ln(\text{hardness}) - 1.03)}$" (see the figure "maximum copper concentration vs. hardness") at any time.


24-HOUR AVERAGE
COPPER CONCENTRATION
VS.
HARDNESS
24-HOUR AVG. COPPER CONC.=$e^{(0.65 \cdot \ln(\text{HARDNESS}) - 1.94)}$
24-HOUR AVERAGE COPPER CONC. (µg/l)
ln scale
20.0
10.0
4.0
2.0
1.0
0.4
0.2
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

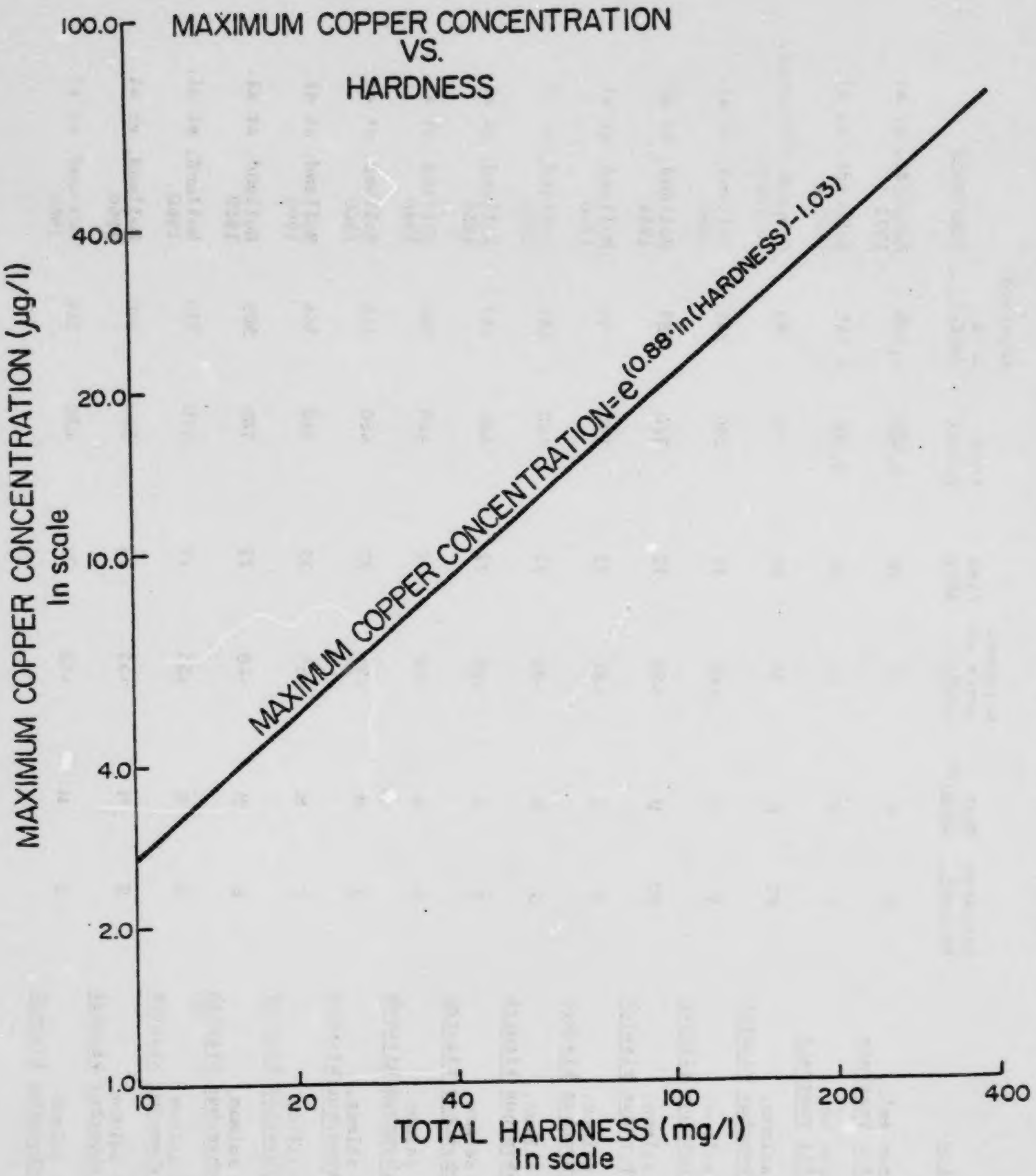

MAXIMUM COPPER CONCENTRATION
VS.
HARDNESS
MAXIMUM COPPER CONCENTRATION=e^(0.88·ln(HARDNESS)-1.03)
MAXIMUM COPPER CONCENTRATION (µg/l)
ln scale
100.0
40.0
20.0
10.0
4.0
2.0
1.0
10
20
40
100
200
400
TOTAL HARDNESS (mg/l)
ln scale

Table 1. Freshwater fish acute values for copper

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
American eel, *Anguilla rostrata*	S	M	53	96	6,400	4,540	Rehwoldt, et al. 1971
American eel, *Anguilla rostrata*	S	M	55	96	6,000	4,260	Rehwoldt, et al. 1972
Coho salmon, *Oncorhynchus kisutch*	FT	M	20	96	43	43	Chapman & Stevens, In press
Coho salmon, *Oncorhynchus kisutch*	S	U	~80	72	280	141	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	FT	U	~80	72	370	262	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	U	~80	72	190	96	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	U	~80	72	480	241	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~40	72	440	287	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~40	72	460	300	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~55	72	480	314	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~55	72	560	366	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~40	72	780	509	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~55	72	510	333	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~55	72	520	340	Holland, et al. 1960
Coho salmon, *Oncorhynchus kisutch*	S	M	~40	72	480	314	Holland, et al. 1960

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Coho salmon (yearling), *Oncorhynchus kisutch*	S	M	89-99	96	74	53	Lorz & McPherson, 1976
Coho salmon (yearling), *Oncorhynchus kisutch*	S	M	89-99	96	70	50	Lorz & McPherson, 1976
Coho salmon (smolt), *Oncorhynchus kisutch*	S	M	89-99	96	60	43	Lorz & McPherson, 1976
Chinook salmon (alevin), *Oncorhynchus tshawytscha*	FT	M	25	96	26	26	Chapman, In press
Chinook salmon (swim-up), *Oncorhynchus tshawytscha*	FT	M	25	96	19	19	Chapman, In press
Chinook salmon (parr), *Oncorhynchus tshawytscha*	FT	M	25	96	38	38	Chapman, In press
Chinook salmon (smolt), *Oncorhynchus tshawytscha*	FT	M	25	96	26	26	Chapman, In press
Chinook salmon, *Oncorhynchus tshawytscha*	FT	M	13	96	10	10	Chapman & McCrady, 1977
Chinook salmon, *Oncorhynchus tshawytscha*	FT	M	46	96	22	22	Chapman & McCrady, 1977
Chinook salmon, *Oncorhynchus tshawytscha*	FT	M	182	96	85	85	Chapman & McCrady, 1977
Chinook salmon, *Oncorhynchus tshawytscha*	FT	M	359	96	130	130	Chapman & McCrady, 1977
Chinook salmon, *Oncorhynchus tshawytscha*	S	M	~80	72	190	124	Holland, 1960
Cutthroat trout, *Salmo clarki*	FT	M	205	96	367***	367	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	70	96	186***	186	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	18	96	36.8***	36.8	Chakoumakos, et al. In press

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cutthroat trout, *Salmo clarki*	FT	M	204	96	232***	232	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	83	96	162***	162	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	31	96	73.6***	73.6	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	160	96	91***	91*	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	74	96	44.4***	44.4	Chakoumakos, et al. In press
Cutthroat trout, *Salmo clarki*	FT	M	26	96	15.7***	15.7	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	30	96	19.9***	19.9	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	32	96	22.4***	22.4	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	31	96	28.9***	28.9	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	31	96	30***	30	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	30	96	30***	30	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	101	96	176***	176	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	101	96	40***	40	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	99	96	33.1***	33.1	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	102	96	30.7***	30.7	Howarth & Sprague, In press

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, *Salmo gairdneri*	FT	M	101	96	46.3***	46.3	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	99	96	47.9***	47.9	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	100	96	48.1***	48.1	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	100	96	81.1***	81.1	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	98	96	85.9***	85.9	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	370	96	232***	232	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	366	96	70***	70	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	371	96	82.2***	82.2	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	361	96	298***	298	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	371	96	516***	516	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	360	96	309***	309	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	364	96	111***	111	Howarth & Sprague, In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	169***	169	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	85.3***	85.3	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	83.3***	83.3	Chakoumakos, et al. In press

Table 1. (Continued)

Organism	Bioassay Method *	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	103***	103	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	274***	274	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	128***	128	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	221***	221	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	165***	165	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	197***	197	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	514***	514	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	194	96	243***	243	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	94	96	62.9***	62.9	Chakoumakos, et al. In press
Rainbow trout, *Salmo gairdneri*	FT	M	177	96	48.9***	48.9	Chakoumakos, et al. In press
Rainbow trout (alvein), *Salmo gairdneri*	FT	M	25	96	28	28	Chapman, In press
Rainbow trout (swim-up), *Salmo gairdneri*	FT	M	25	96	17	17	Chapman, In press
Rainbow trout (parr), *Salmo gairdneri*	FT	M	25	96	18	18	Chapman, In press
Rainbow trout (smolt), *Salmo gairdneri*	FT	M	25	96	29	29	Chapman, In press
Rainbow trout, *Salmo gairdneri*	FT	M	42	96	57	57	Chapman & Stevens, In press

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rainbow trout, Salmo gairdneri	S	M	36	24	950	445	Cairns, et al. 1978
Rainbow trout, Salmo gairdneri	S	M	36	24	430	201	Cairns, et al. 1978
Rainbow trout, Salmo gairdneri	S	M	36	24	150	70	Cairns, et al. 1978
Rainbow trout, Salmo gairdneri	FT	M	350	96	102	102	Fogels & Sprague, 1977
Rainbow trout, Salmo gairdneri	FT	M	-	96	253	253	Hale, 1977
Rainbow trout, Salmo gairdneri	FT	U	360-369	96	250-680	193-524	Lett, et al. 1976
Rainbow trout, Salmo gairdneri	Field	M	21-26	48	70	57	Calamari & Marchetti, 1975
Rainbow trout, Salmo gairdneri	S	M	290	96	890	632	Calamari & Marchetti, 1973
Rainbow trout, Salmo gairdneri	FT	-	100	96	250	250	Goettl, et al. 1972
Rainbow trout, Salmo gairdneri	S	M	-	24	140	66	Shaw & Brown, 1974
Rainbow trout, Salmo gairdneri	S	M	-	24	130	61	Shaw & Brown, 1974
Rainbow trout, Salmo gairdneri	S	M	250	72	580	379	Brown, et al. 1974
Rainbow trout, Salmo gairdneri	S	U	320	48	500	221	Brown, 1968
Rainbow trout, Salmo gairdneri	R	M	240	48	750	431	Brown & Dalton, 1970
Rainbow trout, Salmo gairdneri	S	U	"soft"	48	150	66	Cope, 1966

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (μg/l)	Adjusted LC50 (μg/l)	Reference
Rainbow trout, *Salmo gairdneri*	S	-	320	72	1,100	720	Lloyd, 1961
Rainbow trout, *Salmo gairdneri*	S	-	320	48	270	155	Herbert & Vandyke, 1964
Atlantic salmon, *Salmo salar*	FT	M	20	96	~48	~48	Sprague, 1964
Atlantic salmon, *Salmo salar*	S	M	8-10	96	125	89	Wilson, 1972
Atlantic salmon, *Salmo salar*	FT	M	14	96	~32	~32	Sprague & Ramsey, 1965
Brook trout, *Salvelinus fontinalis*	FT	M	45	96	100	100	McKim & Benoit, 1971
Stoneroller, *Campostoma anomalum*	FT	M	200	96	290	290	Geckler, et al. 1976
Stoneroller, *Campostoma anomalum*	FT	M	318	96	340***	340	Geckler, et al. 1976
Goldfish, *Carassius auratus*	S	U	20	96	36	20	Pickering & Henderson, 1966
Goldfish, *Carassius auratus*	S	M	40	24	2,700	1,270	Cairns, et al. 1978
Goldfish, *Carassius auratus*	S	M	40	24	2,900	1,360	Cairns, et al. 1978
Goldfish, *Carassius auratus*	S	M	40	24	1,510	708	Cairns, et al. 1978
Carp, *Cyprinus carpio*	S	M	53	96	810	575	Rehwoldt, et al. 1971
Carp, *Cyprinus carpio*	S	M	55	96	800	568	Rehwoldt, et al. 1972
Golden shiner, *Notemigonius chrysoleucas*	S	M	36	24	330	155	Cairns, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Golden shiner, Notemigonius chrysoleucas	S	M	36	24	230	108	Cairns, et al. 1978
Golden shiner, Notemigonius chrysoleucas	S	M	36	24	270	127	Cairns, et al. 1978
Striped shiner, Notropis chrysocephalus	FT	M	200	96	790	790	Geckler, et al. 1976
Striped shiner, Notropis chrysocephalus	FT	M	200	96	1,900	1,900	Geckler, et al. 1976
Striped shiner, Notropis chrysocephalus	FT	M	314	96	720***	720	Geckler, et al. 1976
Striped shiner, Notropis chrysocephalus	FT	M	303	96	1,100***	1,100	Geckler, et al. 1976
Striped shiner, Notropis chrysocephalus	FT	M	318	96	630***	630	Geckler, et al. 1976
Striped shiner, Notropis chrysocephalus	FT	M	316	96	680***	680	Geckler, et al. 1976
Striped shiner, Notropis chrysocephalus	FT	M	274	96	690***	690	Geckler, et al. 1976
Bluntnose minnow, Pimephales notatus	S	M	324	24	430***	201	Geckler, et al. 1976
Bluntnose minnow, Pimephales notatus	S	M	318	24	420***	197	Geckler, et al. 1976
Bluntnose minnow, Pimephales notatus	S	M	318	24	300***	141	Geckler, et al. 1976
Bluntnose minnow, Pimephales notatus	S	M	314	24	320***	150	Geckler, et al. 1976
Bluntnose minnow, Pimephales notatus	S	M	318	24	330***	155	Geckler, et al. 1976
Bluntnose minnow, Pimephales notatus	S	M	324	24	420***	197	Geckler, et al. 1976

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluntnose minnow, *Pimephales notatus*	S	M	310	24	330***	145	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	296	24	370***	173	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	308	24	340***	159	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	314	24	400***	187	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	315	24	390***	183	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	200	24	150***	70	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	200	96	290	290	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	200	96	260	260	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	200	96	260	260	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	200	96	280	280	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	200	96	340	340	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	314	96	390	390	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	303	96	620***	620	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	303	96	450***	320	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	S	M	303	96	470***	334	Geckler, et al. 1976

Table 1. (Continued)

Organism	Bioassay Method *	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluntnose minnow, *Pimephales notatus*	FT	M	318	96	480***	480	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	316	96	570***	570	Geckler, et al. 1976
Bluntnose minnow, *Pimephales notatus*	FT	M	194	96	210	210	Horning & Neiheisel, In press
Bluntnose minnow, *Pimephales notatus*	FT	M	194	96	220	220	Horning & Neiheisel, In press
Bluntnose minnow, *Pimephales notatus*	FT	M	194	96	270	270	Horning & Neiheisel, In press
Fathead minnow, *Pimephales promelas*	FT	M	202	96	460	460	Pickering, et al. 1977
Fathead minnow, *Pimephales promelas*	FT	M	202	96	490	490	Pickering, et al. 1977
Fathead minnow, *Pimephales promelas*	FT	M	200	96	790***	790	Andrew, 1976
Fathead minnow, *Pimephales promelas*	FT	M	45	96	200***	200	Andrew, 1976
Fathead minnow, *Pimephales promelas*	S	U	360	96	1,450	793	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S	U	20	96	23	13	Pickering & Henderson, 1966
Fathead minnow, *Pimephales promelas*	S	U	400	96	1,400	765	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S	U	20	96	50	27	Tarzwell & Henderson, 1960
Fathead minnow, *Pimephales promelas*	S	U	200	96	430	235	Mount, 1968
Fathead minnow, *Pimephales promelas*	FT	M	200	96	470	470	Mount & Stephan, 1969

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc. **	Hardness (mg/l as CaCO$_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, *Pimephales promelas*	S	U	31	96	84	46	Mount & Stephan, 1969
Fathead minnow, *Pimephales promelas*	FT	M	31	96	75	75	Mount & Stephan, 1969
Fathead minnow, *Pimephales promelas*	S	M	280	96	750***	533	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	244	96	750***	533	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	212	96	600***	426	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	260	96	820***	582	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	224	96	980***	696	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	228	96	830***	589	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	150	96	930***	660	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	310	96	870***	618	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	294	96	730***	518	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	308	96	840***	596	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	280	96	770***	547	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	280	96	630***	447	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	120	96	690***	490	Brungs, et al. 1976

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, *Pimephales promelas*	S	M	298	96	860***	611	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	200	96	440	440	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	200	96	490	490	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	314	96	540***	540	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	303	96	1,000***	1,000	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	318	96	670***	670	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	318	96	740***	525	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	316	96	865***	865	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	S	M	316	96	1,300***	923	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	274	96	610***	610	Geckler, et al. 1976
Fathead minnow, *Pimephales promelas*	FT	M	48	96	114	114	Lind, et al. Manuscript
Fathead minnow, *Pimephales promelas*	FT	M	45	96	121	121	Lind, et al. Manuscript
Fathead minnow, *Pimephales promelas*	FT	M	46	96	88.5	88.5	Lind, et al. Manuscript

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Fathead minnow, Pimephales promelas	FT	M	30	96	436	436	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	37	96	516	516	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	87	96	1,586	1,586	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	73	96	1,129	1,129	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	84	96	550	550	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	66	96	1,001	1,101	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	117	96	2,050	2,050	Lind, et al. Manuscript
Fathead minnow, Pimephales promelas	FT	M	121	96	2,336	2,336	Lind, et al. Manuscript
Blacknose dace, Rhinichthys atratulus	FT	M	200	96	320	320	Geckler, et al. 1976
Creek chub, Semotilus atromaculatus	FT	M	200	96	310	310	Geckler, et al. 1976
Creek chub, Semotilus atromaculatus	FT	M	316	96	1,050***	1,050	Geckler, et al. 1976
Creek chub, Semotilus atromaculatus	FT	M	274	96	340***	340	Geckler, et al. 1976
Brown bullhead, Ictalurus nebulosus	FT	M	200	96	180	180	Brungs, et al. 1973
Brown bullhead, Ictalurus nebulosus	FT	M	200	96	540	540	Geckler, et al. 1976
Brown bullhead, Ictalurus nebulosus	FT	M	303	96	570***	570	Geckler, et al. 1976
Channel catfish, Ictalurus punctatus	S	M	36	24	3,700	1,730	Cairns, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Channel catfish, *Ictalurus punctatus*	S	M	36	24	2,600	1,220	Cairns, et al. 1978
Channel catfish, *Ictalurus punctatus*	S	M	36	24	3,100	1,450	Cairns, et al. 1978
Banded killifish, *Fundulus diaphanus*	S	M	53	96	860	611	Rehwoldt, et al. 1971
Banded killifish, *Fundulus diaphanus*	S	M	55	96	840	596	Rehwoldt, et al. 1972
Flagfish, *Jordanella floridae*	FT	M	350-375	96	1,270	1,270	Fogels & Sprague, 1977
Guppy, *Poecilia reticulata*	S	U	20	96	36	20	Pickering & Henderson, 1966
Guppy, *Poecilia reticulata*	S	U	76	24	1,250	450	Minicucci, 1971
Guppy, *Poecilia reticulata*	FT	M	87.5	96	112	112	Chynoweth, et al. 1976
Guppy, *Poecilia reticulata*	FT	M	67.2	96	138	138	Chynoweth, et al. 1976
White perch, *Morone americanus*	S	M	53	96	6,200	4,400	Rehwoldt, et al. 1971
White perch, *Morone americanus*	S	M	55	96	6,400	4,540	Rehwoldt, et al. 1972
Striped bass, *Morone saxatilis*	S	M	53	96	4,300	3,050	Rehwoldt, et al. 1971
Striped bass, *Morone saxatilis*	S	M	55	96	4,000	2,840	Rehwoldt, et al. 1972
Striped bass, *Morone saxatilis*	S	U	35	96	620	339	Wellborn, 1969
Striped bass (larva), *Morone saxatilis*	S	U	68.4	96	50	27	Hughes, 1973
Striped bass (larva), *Morone saxatilis*	S	U	68.4	96	100	55	Hughes, 1971

Table 1 (Continued)

Organism	Bioassay Method *	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Striped bass (fingerling), Morone saxitilis	S	U	68.4	96	150	82	Hughes, 1971
Rainbow darter, Etheostoma caeruleum	FT	M	200	96	320	320	Geckler, et al. 1976
Rainbow darter, Etheostoma caeruleum	FT	M	318	96	630***	630	Geckler, et al. 1976
Rainbow darter, Etheostoma caeruleum	FT	M	316	96	610***	610	Geckler, et al. 1976
Rainbow darter, Etheostoma caeruleum	FT	M	274	96	500***	500	Geckler, et al. 1976
Johnny darter, Etheostoma nigrum	FT	M	316	96	610***	610	Geckler, et al. 1976
Orangethroat darter, Etheostoma spectabile	FT	M	200	96	850	850	Geckler, et al. 1976
Orangethroat darter, Etheostoma spectabile	FT	M	303	96	590***	590	Geckler, et al. 1976
Orangethroat darter, Etheostoma spectabile	FT	M	318	96	620***	620	Geckler, et al. 1976
Orangethroat darter, Etheostoma spectabile	FT	M	316	96	760***	760	Geckler, et al. 1976
Orangethroat darter, Etheostoma spectabile	FT	M	274	96	700***	700	Geckler, et al. 1976
Rock bass, Ambloplites reipestris	FT	M	24	96	1,432	1,432	Lind, et al. Manuscript
Pumpkinseed, Lepomis gibbosus	S	-	53	96	2,400	1,700	Rehwoldt, et al. 1971
Pumpkinseed, Lepomis gibbosus	S	-	55	96	2,700	1,920	Rehwoldt, et al. 1972
Bluegill, Lepomis macrochirus	FT	M	45	96	1,100	1,100	Benoit, 1975
Bluegill, Lepomis macrochirus	S	M	36	24	2,590	1,210	Cairns, et al. 1978

Table 1. (Continued)

Organism	Bioassay Method*	Test Conc**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bluegill, *Lepomis macrochirus*	S	M	36	24	2,500	1,170	Cairns, et al. 1978
Bluegill, *Lepomis macrochirus*	S	M	36	24	3,820	1,790	Cairns, et al. 1978
Bluegill, *Lepomis macrochirus*	S	-	-	48	2,800	1,610	Cope, 1966
Bluegill, *Lepomis macrochirus*	FT	M	316	96	4,300***	4,300	Geckler, et al. 1976
Bluegill, *Lepomis macrochirus*	FT	M	318	96	4,250***	4,250	Geckler, et al. 1976
Bluegill, *Lepomis macrochirus*	FT	M	200	96	8,300	8,300	Geckler, et al. 1976
Bluegill, *Lepomis macrochirus*	FT	M	200	96	10,000	10,000	Geckler, et al. 1976
Bluegill, *Lepomis macrochirus*	S	-	43	96	1,250	890	Patrick, et al. 1968
Bluegill, *Lepomis macrochirus*	S	U	20	96	660	360	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S	U	360	96	10,200	5,580	Pickering & Henderson, 1966
Bluegill, *Lepomis macrochirus*	S	-	45-47	96	740	525	Trama, 1954
Bluegill, *Lepomis macrochirus*	S	U	101	96	1,800	980	Turnbull, et al. 1954
Bluegill, *Lepomis macrochirus*	FT	U	35	96	2,400	1,850	O'Hara, 1971

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* S = static, FT = flow-through, R = renewal

** U = unmeasured, M = measured

***Results are for dissolved copper.

Table 1. (Continued)

Organism	Bioassay Method	Test Conc.	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference

Adjusted LC50 vs. hardness

Chinook salmon: slope = 0.72, intercept = 0.83, r = 0.88, p = 0.01, N = 9

Cutthroat trout: slope = 0.88, intercept = 0.79, r = 0.78, p = 0.01, N = 9

Rainbow trout: slope = 0.75, intercept = 1.05, r = 0.69, p = 0.01, N = 56

Fathead minnow: slope = 0.77, intercept = 2.27, r = 0.66, p = 0.01, N = 46

Bluegill: slope = 0.84, intercept = 3.86, r = 0.83, p = 0.01, N = 14

Geometric mean slope = 0.79

Mean intercept for 29 fish species = 2.48

Adjusted mean intercept = 2.48 - $\ln(3.9)$ = 1.12

Final Fish Acute Value = $e^{(0.72 \cdot \ln(\text{hardness} + 0.83)}$ from chinook salmon.

Table 2. Freshwater invertebrate acute values for copper

Organism	Bioassay Method*	Test Conc. **	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Annelid worm, *Aeolosoma headleyi*	S	M	45	48	2,600	1,230	Cairns, et al. 1978
Annelid worm, *Aeolosoma headleyi*	S	M	45	48	2,300	1,090	Cairns, et al. 1978
Annelid worm, *Aeolosoma headleyi*	S	M	45	48	2,000	950	Cairns, et al. 1978
Annelid worm, *Aeolosoma headleyi*	S	M	45	48	1,650	780	Cairns, et al. 1978
Annelid worm, *Aeolosoma headleyi*	S	M	45	48	1,000	470	Cairns, et al. 1978
Worm, *Limnodrilus hoffmeisteri*	S	U	100	96	102	86	Wurtz & Bridges, 1961
Worm, *Nais* sp.	S	M	50	96	90	99	Rehwoldt, et al. 1973
Snail (egg), *Amnicola* sp.	S	M	50	96	9,300	10,200	Rehwoldt, et al. 1973
Snail (adult), *Amnicola* sp.	S	M	50	96	900	990	Rehwoldt, et al. 1973
Snail, *Campeloma decisum*	FT	M	35-55	96	1,700	1,700	Arthur & Leonard, 1970
Snail, *Goniobasis livescens*	S	-	137-171	48	860	407	Cairns, et al. 1976
Snail, *Gyraulus circumstriatris*	S	U	100	96	108	91	Wurtz & Bridges, 1961
Snail, *Lymnea emarginata*	S	-	137-171	48	300	142	Cairns, et al. 1976
Snail, *Nitrocris* sp.	S	M	45	48	3,000	1,420	Cairns, et al. 1978
Snail, *Nitrocris* sp.	S	M	45	48	2,400	1,140	Cairns, et al. 1978

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc*	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Snail, *Nitrocris* sp.	S	M	45	48	1,000	470	Cairns, et al. 1978
Snail, *Nitrocris* sp.	S	M	45	48	300	142	Cairns, et al. 1978
Snail, *Nitrocris* sp.	S	M	45	48	210	99	Cairns, et al. 1978
Snail, *Physa heterostropha*	S	U	100	96	69	85	Wurtz & Bridges, 1961
Snail, *Physa integra*	FT	M	35-55	96	39	39	Arthur & Leonard, 1970
Cladoceran, *Daphnia hyalina*	S	U	66	48	5	4.2	Baudouin & Scoppa, 1974
Cladoceran, *Daphnia magna*	S	U	226	48	200	169	Cabejszek & Stasiak, 1960
Cladoceran, *Daphnia magna*	R	U	45.3	48	9.8	8.3	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	R	U	45.3	48	60	51	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	S	U	99	48	65	55	Adema & Degroot-Van Zijl, 1972
Cladoceran, *Daphnia magna*	S	U	99	48	30	25	Adema & Degroot-Van Zijl, 1972
Cladoceran, *Daphnia magna*	S	U	~120	48-64	12.7	10.8	Anderson, 1948
Cladoceran, *Daphnia magna*	S	U	-	48	100	85	Bringmann & Kuhn, 1959

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, *Daphnia magna*	S	U	45	48	90	76	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	S	U	45	48	70	59	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	S	U	45	48	40	34	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	S	U	45	48	10	8.5	Cairns, et al. 1978
Cladoceran, *Daphnia magna*	S	U	45	48	7	5.9	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	S	U	45	48	70	59	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	S	U	45	48	60	51	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	S	U	45	48	20	17	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	S	U	45	48	10	8.5	Cairns, et al. 1978
Cladoceran, *Daphnia pulex*	S	U	45	48	5.6	4.7	Cairns, et al. 1978
Cladoceran, *Daphnia pulicaria*	R	M	48	48	11.4	12.5	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	48	48	9.06	10	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	48	48	7.24	8	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	44	48	10.8	11.9	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	31	48	55.5	61.1	Lind, et al. Manuscript

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, *Daphnia pulicaria*	R	M	29	48	55.3	60.8	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	28	48	53.3	58.6	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	~88	48	97.2	107	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	100	48	199	219	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	86	48	627	690	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	82	48	213	234	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	84	48	165	182	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	16	48	35.5	39.1	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	151	48	78.8	86.7	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	96	48	113	124	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	26	48	76.4	84	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	84	48	84.7	93.2	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	92	48	184	202	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	106	48	240	294	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	45	48	9.3	10.2	Lind, et al. Manuscript
Cladoceran, *Daphnia pulicaria*	R	M	95	48	17.8	19.6	Lind, et al. Manuscript

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Cladoceran, Daphnia pulicaria	R	M	145	48	23.7	26.1	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	R	M	245	48	27.3	30.0	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	R	M	95	48	25.2	27.7	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	R	M	145	48	25.1	27.6	Lind, et al. Manuscript
Cladoceran, Daphnia pulicaria	R	M	245	48	25.1	27.6	Lind, et al. Manuscript
Copepod, Cyclops abyssorum	S	U	66	48	2,500	2,120	Baudouin & Scoppa, 1974
Copepod, Eudiaptomus padanus	S	U	66	48	500	424	Baudouin & Scoppa, 1974
Scud, Gammarus lacustris	S	U	-	96	1,500	1,270	Nebeker & Gaufin, 1964
Scud, Gammarus pseudolimnea	FT	M	35-55	96	20	20	Arthur & Leonard, 1970
Scud, Gammarus sp.	S	M	50	96	910	1,000	Rehwoldt, et al. 1973
Crayfish, Orconectes rusticus	FT	M	100-125	96	3,000	3,000	Hubshman 1967
Mayfly, Ephemerella subvaria	S	M	40	48	320	151	Warnick & Bell, 1969
Stonefly, Acroneuria lycorias	S	M	40	96	8,300	9,130	Warnick & Bell, 1969
Damselfly, Unidentified	S	M	50	96	4,600	5,060	Rehwoldt, et al. 1973
Midge, Chironomus sp.	S	M	50	96	30	33	Rehwoldt, et al. 1973
Caddisfly, Unidentified	S	M	50	96	6,200	6,820	Rehwoldt, et al. 1973

Table 2. (Continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Rotifer, *Philodina acuticornis*	S	M	45	48	1,300	1,430	Cairns, et al. 1978
Rotifer, *Philodina acuticornis*	S	M	45	48	1,200	1,320	Cairns, et al. 1978
Rotifer, *Philodina acuticornis*	S	M	45	48	1,130	1,240	Cairns, et al. 1978
Rotifer, *Philodina acuticornis*	S	M	45	48	1,000	1,100	Cairns, et al. 1978
Rotifer, *Philodina acuticornis*	S	M	45	48	950	1,050	Cairns, et al. 1978
Rotifer, *Philodina acuticornis*	S	M	40	96	160	176	Buikema, et al. 1977
Rotifer, *Philodina acuticornis*	R	U	25	96	700	593	Buikema, et al. 1974
Rotifer, *Philodina acuticornis*	R	U	81	96	1,100	932	Buikema, et al. 1974

* S = static, FT = flow-through, R = renewal

** U = unmeasured, M = measured

Adjusted LC50 vs. hardness

Daphnia magna: slope = 0.75, intercept = 0.19, r = 0.39, not significant, N = 11

Daphnia pulicaria: slope = 1.03, intercept = 0.11, r = 0.51, p = 0.05, N = 19

Geometric mean slope = 0.88

Mean intercept for 26 species = 2.01

Adjusted mean intercept = 2.01 - ln(21) = -1.03

Final Invertebrate Acute Value = $e^{(0.88 \cdot \ln(\text{hardness}) - 1.03)}$

Table 3. Freshwater fish chronic values for copper

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
Rainbow trout, *Salmo gairdneri*	E-L	12-19	7.5	-	Goettl, et al. 1974
Rainbow trout, *Salmo gairdneri*	E-L	11.4-31.7	9.5	45.4	McKim, et al. In press
Brown trout, *Salmo trutta*	E-L	22.0-43.2	15.4	45.4	McKim, et al. In press
Brook trout, *Salvelinus fontinalis*	LC	9.5-17.4	12.9	45	McKim & Benoit, 1971
Brook trout, *Salvelinus fontinalis*	E-L	22.3-43.5	15.6	45.4	McKim, et al. In press
Brook trout, *Salvelinus fontinalis*	E-L	3-5	1.9	37.5	Sauter, et al. 1976
Brook trout, *Salvelinus fontinalis*	E-L	5-8	3.2	187	Sauter, et al. 1976
Lake trout, *Salvelinus namaycush*	E-L	22.0-42.3	15.3	45.4	McKim, et al. In press
Northern pike, *Esox lucius*	E-L	34.9-104.4	30.2	45.4	McKim, et al. In press
Bluntnose minnow, *Pimephales notatus*	LC	4.3-18	8.8	194	Horning & Neiheisel, In press
Fathead minnow, *Pimephales promelas*	LC	14.5-33	21.9	198	Mount, 1968
Fathead minnow, *Pimephales promelas*	LC	106-18.4	14.0	30	Mount & Stephan, 1969
Fathead minnow, *Pimephales promelas*	LC	24-32	27.7	200	Pickering, et al. 1977
Fathead minnow, *Pimephales promelas*	LC	57-100	75.4	274	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	E-L	13.1-26.2	9.3	45	Lind, et al. Manuscript

Table 3. (Continued)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
White sucker, *Catostomus commersoni*	E-L	12.9-33.8	10.4	45.4	McKim, et al. In press
Channel catfish, *Ictalurus punctatus*	E-L	12-18	7.3	36	Sauter, et al. 1976
Channel catfish, *Ictalurus punctatus*	E-L	13-19	7.9	186	Sauter, et al. 1976
Bluegill, *Lepomis macrochirus*	LC	21-40	29.0	45	Benoit, 1975
Walleye, *Stizostedion vitreum*	E-L	13-21	16.5	35	Sauter, et al. 1976

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* E-L = embryo-larval, LC = life cycle or partial life cycle

Fish chronic value vs. hardness

Fathead minnow: slope = 0.65, intercept = 0.071, r = 0.82, not significant, N = 5

Geometric mean slope = 0.65 (only value available)

Mean intercept for 11 fish species = -0.042

Adjusted mean intercept = -0.042 - ln(6.7) = -1.94

Final Fish Chronic Value = $e^{(0.65 \cdot \ln(\text{hardness}) - 1.94)}$

Table 3. (Continued)

Application Factor Values

Species	96-hr LC50 (µg/l)	MATC (µg/l)	AF	Reference
Brook trout, *Salvelinus fontinalis*	100	9.5-17.4	0.13	McKim & Benoit, 1971
Bluntnose minnow, *Pimephales notatus*	230	4.3-18	0.038	Horning & Neiheisel, In press
Fathead minnow, *Pimephales promelas*	470	14.5-33	0.046	Mount, 1968
Fathead minnow, *Pimephales promelas*	75	10.6-18.4	0.19	Mount & Stephan, 1969
Fathead minnow, *Pimephales promelas*	790	57-100	0.096	Brungs, et al. 1976
Fathead minnow, *Pimephales promelas*	475	24-32	0.058	Pickering, et al. 1977
Bluegill, *Lepomis macrochirus*	1,100	21-40	0.026	Benoit, 1975

Geometric mean AF = 0.067

Table 4. Freshwater invertebrate chronic values for copper

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)	Hardness (mg/l as $CaCO_3$)	Reference
Snail, Campeloma decisum	LC	8-14.8	10.9	45	Arthur & Leonard, 1970
Snail, Physa integra	LC	8-14.8	10.9	45	Arthur & Leonard, 1970
Cladoceran, Daphnia magna	LC	22-35	27.7	45.3	Biesinger & Christensen, 1972
Cladoceran, Daphnia magna	LC	20-40	28.2	145	Winner, et al. 1977
Cladoceran, Daphnia magna	LC	20-40	28.2	145	Winner, et al. 1977
Cladoceran, Daphnia magna	LC	20-40	28.2	145	Winner, et al. 1977
Cladoceran, Daphnia magna	LC	40-60	49.0	145	Winner & Farrell, 1976
Cladoceran, Daphnia pulex	LC	40-60	49.0	145	Winner & Farrell, 1976
Cladoceran, Daphnia parvula	LC	40-60	49.0	145	Winner & Farrell, 1976
Cladoceran, Daphnia ambigua	LC	40-60	49.0	145	Winner & Farrell, 1976
Amphipod, Gammarus pseudolimnaeus	LC	4.6-8	6.1	45	Arthur & Leonard, 1970

* LC = life cycle or partial life cycle

Invertebrate chronic value vs. hardness

No hardness relationship could be derived for any invertebrate species.

Slope = 0.65 from fish chronic values.

Mean intercept for 7 invertebrate species = 0.21

Adjusted mean intercept = 0.21 - ln(5.1) = -1.42

Final Invertebrate Chronic Value = $e^{(0.65 \cdot \ln(\text{hardness}) -1.42)}$

Table 5. Freshwater plant effects for copper

Organism	Effect	Concentration (ug/l)	Reference
Alga, *Anabaena flos-aqua*	75% growth inhibition	200	Young & Lisk, 1972
Alga, *Anabaena variabilis*	Growth inhibition	100	Young & Lisk, 1972
Alga, *Anacystis nidulans*	Growth inhibition	100	Young & Lisk, 1972
Alga, *Chlamydomonas* sp.	Growth reduction	8,000	Cairns, et al. 1978
Alga, *Chlorella pyrenoidosa*	Lag in growth	1	Steeman-Nielsen & Wium-Andersen, 1970
Alga, *Chlorella pyrenoidosa*	Growth inhibition	100	Steeman-Nielsen & Kamp-Nielsen, 1970
Alga, *Chlorella regularis*	Lag in growth	20	Sakaguchi, et al. 1977
Alga, *Chlorella* sp.	Photosynthesis inhibited	6.3	Gachter, et al. 1973
Alga, *Chlorella vulgaris*	Growth inhibition	200	Young & Lisk, 1972
Alga, *Chlorella vulgaris*	EC50 growth, 33 days	180	Rosko & Rachlin, 1977
Alga, *Chlorella vulgaris*	50% growth reduction	100-200	Stokes & Hutchinson, 1976
Alga, *Cyclotella meneghiniana*	Growth reduction	8,000	Cairns, et al. 1978
Alga, *Eudorina californica*	Growth inhibition	5,000	Young & Lisk, 1972
Alga, *Scenedesmus acuminatus*	40% growth reduction	300	Stokes & Hutchinson, 1976
Alga, *Scenedesmus quadricauda*	Threshold toxicity	150	Bringman & Kuhn, 1959
Alga, *Scenedesmus quadricauda*	Growth reduction	8,000	Cairns, et al. 1978

Table 5. (Continued)

Organism	Effect	Concentration (μg/l)	Reference
Algae, Mixed culture	Significant reduction in photosynthesis	5	Elder & Horne, 1978
Blue green algae, Mixed culture	50% reduction in phosotynthesis	25	Steeman-Nielsen & Bruun-Laursen, 1976
Diatom, *Nitzschia linearis*	TLM-120 hr	795-815	Patrick, et al. 1968
Diatom, *Nitzschia palea*	Complete growth inhibition	5	Steeman-Nielsen & Wium-Anderson, 1970
Duckweed, *Lemna minor*	EC50, 7 day	119	Walbridge, 1977
Eurasian watermilfoil, *Myriophyllum spicatum*	50% root weight reduction	250	Stanley, 1974
Green alga, *Selanastrum capriconutum*	Growth reduction	50	Bartlett, et al., 1974

Final plant value = 1 μg/l

Table 6. Freshwater residues for copper

Organism	Bioconcentration Factor	Time (days)	Reference
Alga, Chlorella regularis	2,000	20 hrs	Sakaguchi, et al. 1977
Stonefly, Pteronarcys californica	203	14 days	Nehring, 1976
Fathead minnow (larva), Pimephales promelas	290	30 days	Lind, et al., Manuscript

Geometric mean bioconcentration factor for all species = 490

Table 7. Other freshwater data for copper

Organism	Test Duration	Effect	Result (ug/l)	Reference
Cladoceran, *Daphnia ambigua*	72 hrs	LC50	67.7	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	life cycle	Reduced number of young produced	10	Winner, et al. 1977
Cladoceran, *Daphnia magna*	life cycle	Reduced number of young produced	10	Winner, et al. 1977
Cladoceran, *Daphnia magna*	life cycle	Reduced number of young produced	10	Adema & DeGroot Van Zijl, 1972
Cladoceran, *Daphnia magna*	72 hrs	LC50	86.5	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	72 hrs	LC50	88.8	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	72 hrs	LC50	85	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	72 hrs	LC50	81.5	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	72 hrs	LC50	81.4	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	72 hrs	LC50	85.3	Winner & Farrell, 1976
Cladoceran, *Daphnia magna*	29 hrs	Median survival time	12.7	Andrew, et al. 1977
Cladoceran, *Daphnia magna*	24 hrs	LC50	80	Bringman & Kuhn, 1977
Cladoceran, *Daphnia parvula*	72 hrs	LC50	57	Winner & Farrell, 1976
Cladoceran, *Daphnia parvula*	72 hrs	LC50	72	Winner & Farrell, 1976
Cladoceran, *Daphnia pulex*	72 hrs	LC50	54	Winner & Farrell, 1976
Cladoceran, *Daphnia pulex*	72 hrs	LC50	86	Winner & Farrell, 1976

Table 7. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Mayfly, *Ephemerella grandis*	14 days	LC50	180-200	Nehring, 1976
Stonefly, *Pteronarcys californica*	14 days	LC50	10,100-13,900	Nehring, 1976
Caddisfly, *Hydropsyche betteni*	14 days	50% survival	32,000	Warnick & Bell, 1969
Crayfish, *Orconectes rusticus*	17 days	Survival of newly hatched young	125	Hubshman, 1967
Coho salmon, *Oncorhynchus kisutch*	96 hrs	Reduced survival on transfer to seawater	30	Lorz & McPherson, 1976
Coho salmon, *Oncorhynchus kisutch*	30 days	LC50	360	Holland, et al., 1960
Sockeye salmon, *Oncorhynchus nerka*	24 hrs	Significant change in corticosteroid (stress)	64	Donaldson & Dye, 1975
Chinook salmon, *Oncorhynchus tshawytscha*	5 days	LC50	178	Holland, et al. 1960
Chinook salmon, *Oncorhynchus tshawytscha*	26 days	Reduced survival and growth of sac fry	21	Hazel & Meith, 1970
Chinook salmon (alevin), *Oncorhynchus tshawytscha*	200 hrs	LC50	20	Chapman, In press
Chinook salmon (alevin), *Oncorhynchus tshawytscha*	200 hrs	LC10	15	Chapman, In press
Chinook salmon (swim-up), *Oncorhynchus tshawytscha*	200 hrs	LC50	19	Chapman, In press

Table 7. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Chinook salmon (swim-up), *Oncorhynchus tshawytscha*	200 hrs	LC10	14	Chapman, In press
Chinook salmon (parr), *Oncorhynchus tshawytscha*	200 hrs	LC50	30	Chapman, In press
Chinook salmon (parr), *Oncorhynchus tshawytscha*	200 hrs	LC10	17	Chapman, In press
Chinook salmon (smolt), *Oncorhynchus tshawytscha*	200 hrs	LC50	26	Chapman, In press
Chinook salmon (smolt), *Oncorhynchus tshawytscha*	200 hrs	LC10	18	Chapman, In press
Rainbow trout, *Salmo gairdneri*	2 hrs	Depressed olfactory response	8	Hara, et al. 1976
Rainbow trout, *Salmo gairdneri*	7 days	LC50	44	Lloyd, 1961
Rainbow trout, *Salmo gairdneri*	21 days	Median period of survival	40	Grande, 1966
Rainbow trout, *Salmo gairdneri*	10 days	Depressed feeding rate and growth	75	Lett, et al. 1976
Rainbow trout, *Salmo gairdneri*	7 days	Median period of survival	44	Lloyd, 1961
Rainbow trout (alevin), *Salmo gairdneri*	186 hrs	LC50	26	Chapman, In press
Rainbow trout (alevin), *Salmo gairdneri*	186 hrs	LC10	19	Chapman, In press
Rainbow trout (swim-up), *Salmo gairdneri*	200 hrs	LC50	17	Chapman, In press

Table 7. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Rainbow trout (swim-up), *Salmo gairdneri*	200 hrs	LC10	9	Chapman, In press
Rainbow trout (parr), *Salmo gairdneri*	200 hrs	LC50	15	Chapman, In press
Rainbow trout (parr), *Salmo gairdneri*	200 hrs	LC10	8	Chapman, In press
Rainbow trout (smolt), *Salmo gairdneri*	200 hrs	LC50	21	Chapman, In press
Rainbow trout (smolt), *Salmo gairdneri*	200 hrs	LC10	7	Chapman, In press
Rainbow trout (smolt), *Salmo gairdneri*	>10 days	Threshold LC50	94	Fogels & Sprague, 1977
Rainbow trout (smolt), *Salmo gairdneri*	14 days	LC50	870	Calamari & Marchetti, 1973
Rainbow trout (fry), *Salmo gairdneri*	1 hr	Avoidance behavior	0.1	Folmar, 1976
Atlantic salmon, *Salmo salar*	7 days	Incipient lethal level	48	Sprague, 1964
Atlantic salmon, *Salmo salar*	7 days	Incipient lethal level	32	Sprague & Ramsay, 1965
Atlantic salmon, *Salmo salar*	21 days	Median period of survival	40	Grande, 1966
Atlantic salmon, *Salmo salar*	27-38 hrs	Median period of survival	50	Zitko & Carson, 1976
Brown trout, *Salmo trutta*	21 days	Median period of survival	~45	Grande, 1966
Brook trout, *Salvelinus fontinalis*	24 hrs	Significant change in cough rate	9	Drummond, et al. 1973
Brook trout, *Salvelinus fontinalis*	21 days	Significant changes in blood chemistry	23	McKim, et al. 1970

Table 7. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Brook trout, *Salvelinus fontinalis*	337 days	Significant changes in blood chemistry	17.4	McKim, et al. 1970
Golden shiner, *Notemigonius chrysoleucas*	94 hrs	Decrease blood osmolarity	2,500	Lewis & Lewis, 1971
Channel catfish, *Ictalurus punctatus*	94 hrs	Decreased blood osmolarity	2,500	Lewis & Lewis, 1971
Flagfish, *Jordanella floridae*	10 days	LC50	680	Fogels & Sprague, 1977
Bluegill, *Lepomis macrochirus*	24-36 hrs	Altered oxygen consumption rate	300	O'Hara, 1971

SALTWATER ORGANISMS

Acute Toxicity

Data for two saltwater fish species and two different life history stages are available (Table 8). Adjusted 96-hour LC50 values range from 21 µg/l for summer flounder embryos (Cardin et al. 1978) to 278 µg/l for the Florida pompano, (Birdsong, et al. 1971. Studies of the effects of salinity on copper toxicity to adult Florida pompano indicate copper is more toxic at 10°/oo than at 30°/oo (Birdsong, et al. 1971).

The species sensitivity factor of 3.7 applied to the geometric mean LC50 (69 µg/l) yields 19 µg/l which is sufficient to protect the species reported in Table 8. This Final Fish Acute Value is also low enough to encompass the tests of even longer duration. For example, Cardin, et al. (1978) obtained an LC50 of 23 µg/l for summer flounder embryos exposed for 144 hours in a flow-through system with measured concentrations (Table 13).

Saltwater invertebrate species are more sensitive to acute copper poisoning than saltwater fishes (Table 9). The invertebrate data include investigations on three phyla: Annelida, Mollusca, and Arthropoda (Crustacea). The adjusted LC50 values ranged from 5 µg/l for Acartia tonsa (Sosnowski, et al. 1979) to 407 µg/l for the polychaete worm, Nereis diversicolor (Jones, et al. 1976). Pesch and Morgan (1978) determined that the 96-hour LC50 value for Neanthes arenaceodentata of 77 µg/l in a flow-through system increased to 200 µg/l in the presence of a sandy sediment. Jones, et al. (1976) indicated that Nereis diversicolor exhibited a variable response to salinity over a range of 5 to 34°/oo with the greatest toxicity occurring at 5°/oo. The lowest reported copper acute toxicity for the bivalve molluscs was 33 µg/l for the soft-shelled clam, Mya arenaria (Eisler, 1977), and the highest was 108 µg/l for the embryo of the American oyster (Calabrese, et al. 1973). Eisler (1977) indicated that the copper sensitivity of Mya arenaria varied according to the seasonal temperature, with copper toxicity being at least 100 times greater at summer temperatures (22°C) than at winter temperatures (4°C) (Table 13). The crustaceans ranged in copper toxicity from the most sensitive of all the saltwater animals tested, Acartia tonsa at 5 µg/l (Sosnowski, et al. 1979) to the least sensitive, larvae of the shore crab Carcinus maenas (Connors, 1972). Sosnowski, et al. (1979) showed that the sensitivity of field populations of Acartia tonsa to copper was strongly correlated with population density and food ration. Cultured A. tonsa manifested a reproducible toxicological response to copper through six generations (Sosnowski and Gentile, 1978). Johnson and Gentile (1979) reported that lobster larvae appear to be twice as sensitive to copper as the adults.

When the geometric mean of 86 µg/l is divided by the species sensitivity factor (49), the result is 1.8 µg/l. The data base (Table 9), contains a flow-through measured toxicity value of 5 µg/l for Acartia tonsa. Using the recommended guideline procedure of selecting the lower of these two values, the Final Invertebrate Acute Value is 1.8 µg/l. All values reported in Table 9 are greater than 1.8 µg/l indicating probable protection of 95 percent of the invertebrate species.

Since the Final Invertebrate Acute Value of 1.8 µg/l is lower than the Final Fish Acute Value of 19 µg/l, the Final Acute Value for saltwater aquatic life is 1.8 µg/l/.

Chronic Toxicity

There were no reported studies on the chronic toxicity of copper to saltwater fishes.

The chronic toxicity of copper to mysid shrimp, Mysidopsis bahia, has been determined from the flow-through, life cycle exposure of this species (Sosnowski and Gentile, 1979). Groups of 20 individuals were reared in each of five copper concentrations for 46 days at 20°C and 30°/oo salinity (Table 10). The biological responses examined included time of appearance of first brood, the number of spawns, and mean brood size and growth. The appearance of eggs in the brood sac was delayed for 6 and 8 days at 77 µg/l and 140 µg/l respectively. Broods developing at 135 µg/l never matured and no spawns were observed at this concentration. The number of spawns recorded at 77 µg/l was significantly ($P<0.05$) lower than at 38 µg/l. There were no statistically significant differences in the number of spawns at control, 24 µg/l, and 38 µg/l. Brood size was significantly ($P<0.05$) reduced at 77 µg/l but not at lower concentrations. No effects on growth were detected at the copper concentrations tested. Based on reproductive data the maximum copper concentration tested resulting in no observable effects is 38 µg/l. The chronic value, 54 µg/l, is the geometric mean of the limits (38-77 µg/l). The chronic value, when divided by the species sensitivity factor (5.1) results in a Final Invertebrate Chronic Value of 11 µg/l. This concentration is higher than the Final Acute Value (1.8 µg/l) based on the invertebrate

invertebrate species. Apparently, this is because the chronic data are for Mysidopsis bahia, one of the more resistant invertebrate species to copper in acute toxicity tests (Table 9).

Plant Effects

The copper EC50 values (Effective Concentration to inhibit 50 percent photosynthesis or growth) are tabulated in Table 11 for one species of macro-algae and eight species of micro-algae. Copper inhibited the growth rate of Thalassiosiria pseudonana and Scrippsiella faeroense at 5 µg/l. Therefore, the Final Plant Value for copper is 5 µg/l and since this is the lowest of the chronic values, it becomes the Final Chronic Value.

Bioconcentration

Copper is an essential element in the respiratory pigments of some saltwater invertebrate species, especially crustaceans. Saltwater plants have enzymes containing copper which are necessary for photosynthesis. However, copper is also bioconcentrated in excess of any known needs by several saltwater species (Table 12). The highest bioconcentration for copper was obtained with the bivalve molluscs. Shuster and Pringle (1969) found that the American oyster could concentrate copper 28,208 times after a 20-week continuous exposure to 50 µg/l. Even though the tissue of the oyster became bluish-green in color, mortalities at this level were only slightly higher than the controls. The polychaete worm, Neanthes arenaceodentate, bioconcentrated copper 2,546 times (Pesch and Morgan, 1978). In a series of measurements with algae by Riley and Roth (1971), the highest reported concentration factor was 617 for Heteromastix longifillis.

There is no Residue Limited Toxicant Concentration (RLTC) for copper because no maximum permissible tissue concentration is available. However, there have been instances recorded that oysters have been unmarketable because of their green appearance due to high copper content.

Miscellaneous

Exposures for longer than the standard 96-hour acute studies have been recorded in Table 13. Most noteworthy are the mortality values reported for the bay scallop, *Argopecten irradians*, by Zaroogian (1978). At a flow-through exposure of 5 µg/l or 10 µg/l all scallops died within 119 or 112 days, respectively. Even though several studies have been reported on the sub-lethal effects on survival, growth and reproduction, the signficance of these effects have yet to be evaluated.

CRITERION FORMULATION

Saltwater-Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of copper.

Final Fish Acute Value = 19 μg/l

Final Invertebrate Acute Value = 1.8 μg/l

Final Acute Value = 1.8 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 11 μg/l

Final Plant Value = 5.0 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 5.0 μg/l

0.44 x Final Acute Value = 0.79 μg/l

It is recognized that the copper criterion approaches the concentrations of dissolved copper reported for saltwater. A concentration of 1 μg/l is common for copper in saltwater, but copper can range over more than one order of magnitude. There is evidence which indicates that, if copper is complexed by organic compounds in saltwater, the toxicity of the metal can be greatly reduced. As a consequence, it is not necessarily the total concentration of copper in saltwater that determines the toxicity to saltwater organisms but the form of the metal that is the toxic component. However, it must be emphasized that any addition of copper to saltwater above the criterion could exceed the chelation capacity and render saltwater toxic.

The maximum concentration of copper is the Final Acute Value of 1.8 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For copper the criterion to protect saltwater aquatic life as derived using the Guidelines is 0.79 µg/l as a 24-hour average and the concentration should not exceed 1.8 µg/l at any time.

Table 8. Marine fish acute values for copper

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Florida pompano, Trachinotus carolinus	S	U	96	360	197	Birdsong, et al. 1971
Florida pompano, Trachinotus carolinus	S	U	96	380	207	Birdsong, et al. 1971
Florida pompano Trachinotus carolinus	S	U	96	510	278	Birdsong, et al. 1971
Summer flounder (embryo), Paralichthys dentatus	S	U	96	38	21	Cardin, et al. 1978

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* S = static

** U = unmeasured

Geometric mean of adjusted values = 69 µg/l $\frac{69}{3.7} = 19$ µg/l

Table 9. Marine invertebrate acute values for copper

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Polychaete worm, *Neanthes arenaceodentata*	FT	M	96	77	77	Pesch & Morgan, 1978
Polychaete worm, *Neanthes arenaceodentata*	FT	M	96	200	200	Pesch & Morgan, 1978
Polycheate worm, *Nereis diversicolor*	S	U	96	200	169	Jones, et al. 1976
Polychaete worm, *Nereis diversicolor*	S	U	96	445	377	Jones, et al. 1976
Polychaete worm, *Nereis diveriscolor*	S	U	96	480	407	Jones, et al. 1976
Polychaete worm, *Nereis diversicolor*	S	U	96	410	347	Jones, et al. 1976
Polychaete worm, *Phyllodoce maculata*	S	U	96	120	102	McLusky & Phillips, 1975
American oyster (larva), *Crassostrea virginica*	S	U	48	128	108	Calabrese, et al. 1973
Black abalone, *Haliotis cracherodii*	S	U	96	50	42	Martin, et al. 1977
Red abalone, *Haliotis rufescens*	S	U	96	65	55	Martin, et al. 1977
Red abalone (larva), *Haliotis rufescens*	S	U	48	114	97	Martin, et al. 1977
Soft shelled clam, *Mya arenaria*	S	U	96	39	33	Eisler, 1977
Calanoid copepod, *Acartia tonsa*	FT	M	72	26	16	Sosnowski, et al. 1979
Calanoid copepod, *Acartia tonsa*	FT	M	72	29	18	Sosnowski, et al. 1979
Calanoid copepod, *Acartia tonsa*	FT	M	72	13	8	Sosnowski, et al. 1979
Calanoid copepod, *Acartia tonsa*	FT	M	72	45	27	Sosnowski, et al. 1979

Table 9. (Continued)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Calanoid copepod, Acartia tonsa	FT	M	72	73	45	Sosnowski, et al. 1979
Calanoid copepod, Acartia tonsa	FT	M	72	9	5	Sosnowski, et al. 1979
Calanoid copepod, Acartia tonsa	S	U	96	17	14	Sosnowski & Gentile, 1978
Calanoid copepod, Acartia tonsa	S	U	96	55	47	Sosnowski & Gentile, 1978
Calanoid copepod, Acartia tonsa	S	U	96	31	26	Sosnowski & Gentile, 1978
Mysid shrimp, Mysidopsis bahia	FT	M	96	195	195	Sosnowski & Gentile, 1979
American lobster (larva), Homarus americanus	S	U	96	48	41	Johnson & Gentile, 1979
Brown shrimp (larva), Crangon crangon	S	U	48	330	120	Connor, 1972
Shore crab (larva), Carcinus maenas	S	U	48	600	218	Connor, 1972

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* S = static, FT = flow-through

** U = unmeasured, M = measured

Geometric mean of adjusted values = 86 µg/l $\frac{86}{49}$ = 1.8 µg/l

Lowest values from a flow-through test with measured concentration = 5 µg/l

Table 10. Marine invertebrate chronic values for copper (Sosnowski & Gentile, 1979)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)
Mysid shrimp, *Mysidopsis bahia*	LC	38-77	54

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* LC = life cycle or partial life cycle

Geometric mean of chronic values = 54 µg/l $\frac{54}{5.1} = 11$ µg/l

Lowest chronic value = 54 µg/l

Table 11. Marine plant effects for copper

Organism	Effect	Concentration (µg/l)	Reference
Alga, giant kelp, *Macrocystis pyrifera*	96-hr EC-50 photosynthesis inactivation	100	Clendenning & North, 1959
Alga, *Thalassiosira pseudonana*	72-hr EC-50 growth rate	5	Erickson, 1972
Alga, *Amphidinium carteri*	14-day EC-50 growth rate	<50	Erickson, et al. 1970
Alga, *Olisthodiscus luteus*	14-day EC-50 growth rate	<50	Erickson, et al. 1970
Alga, *Skeletonema costatum*	96-hr EC-50 growth rate	10	Jensen, et al. 1970
Alga, *Nitschia closterium*	96-hr EC-50 growth rate	33	Rosko & Rachlin, 1975
Alga, *Scrippsiella faeroense*	5-day EC-50 growth rate	5	Saifullah, 1978
Alga, *Prorocentrum micans*	5-day EC-50 growth rate	10	Saifullah, 1978
Alga, *Gymnodinium splendens*	5-day EC-50 growth rate	20	Saifullah, 1978

Lowest plant value = 5 µg/l

Table 12. Marine residues for copper

Organism	Bioconcentration Factor	Time (days)	Reference
Polychaete worm, *Cirriformia spirabracha*	250*	24	Milanovich, et al. 1976
Polychaete worm, *Neanthes arenaceodentata*	2,546*	28	Pesch & Morgan, 1978
Polychaete worm, *Nereis diversicolor*	203*	24	Jones, et al. 1976
Polychaete wrom, *Phyllodoce maculata*	1,746*	21	McLusky & Phillips, 1975
Bay scallop, *Argopecten irradians*	3,310	112	Zaroogian, 1978
Bay scallop, *Argopecten irradians*	4,155	112	Zaroogian, 1978
American oyster, *Crassostrea virginica*	28,208	140	Shuster & Pringle, 1969
American oyster, *Crassostrea virginica*	20,688	140	Shuster & Pringle, 1969
Northern quahaug, *Mercenaria mercenaria*	88	70	Shuster & Pringle, 1968
Soft shelled clam, *Mya arenaria*	3,300	35	Shuster & Pringle, 1968
Mussel, *Mytilus edulis*	208	112	Zaroogian, 1978
Mussel, *Mytilus edulis*	108	112	Zaroogian, 1978
Mussel, *Mytilus edulis*	90	14	Phillips, 1976
Mussel, *Mytilus galloprovincialis*	800	25	Majori & Petronio, 1973
Alga, *Dunaliella primolecta*	153*	25	Riley & Roth, 1971

Table 12. (Continued)

Organism	Bioconcentration Factor	Time (days)	Reference
Alga, Dunaliella tertiolecta	168*	25	Riley & Roth, 1971
Alga, Chlamydomonas sp.	1[illegible]5*	25	Riley & Roth, 1971
Alga, Chlorella salina	74*	25	Riley & Roth, 1971
Alga, Stichococcus bacillaris	156*	25	Riley & Roth, 1971
Alga, Hemiselmis virescens	273*	25	Riley & Roth, 1971
Alga, Hemiselmis brunescens	553*	25	Riley & Roth, 1971
Alga, Olisthodiscus luteus	182*	25	Riley & Roth, 1971
Alga, Asterionella japonica	309*	25	Riley & Roth, 1971
Alga, Phaeodactylum tricornutum	323*	25	Riley & Roth, 1971
Alga, Monochrysis lutheri	138*	25	Riley & Roth, 1971
Alga, Pseudopedinella pyriformis	85*	25	Riley & Roth, 1971
Alga, Heteromastix longifillis	617*	25	Riley & Roth, 1971
Alga, Micromonas squamata	279*	25	Riley & Roth, 1971
Alga, Tetraselmis tetrathele	265*	25	Riley & Roth, 1971

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* Dry weight to wet weight conversion
Geometric mean bioconcentration factor for all species - 382.

Table 13. Other marine data for copper

Organism	Test Duration	Effect	Result (ug/l)	Reference
Colonial hydroid, *Campanularia flexuosa*	11 days	Growth rate inhibition	10-13	Stebbing, 1976
Colonial hydroid, *Campanularia flexuosa*	--	Enzyme inhibition	1.43	Moore & Stebbing, 1976
Colonial hydroid, *Eirene viridula*	14-21 days	Growth rate inhibition	30-60	Karbe, 1972
Polychaete worm, *Cirriformia spirabracha*	26 days	50% mortality	40	Milanovich, et al. 1976
Polychaete worm, *Phyllodoce maculata*	9 days	50% mortality	80	McLusky & Phillips, 1975
Polychaete worm, *Neanthes arenaceodentata*	28 days	50% mortality	44	Pesch & Morgan, 1978
Polychaete worm, *Neanthes arenaceodentata*	28 days	50% mortality	100	Pesch & Morgan, 1978
Bay scallop, *Argopecten irradians*	112 days	100% mortality	10	Zaroogian, 1978
Bay scallop, *Argopecten irradians*	119 days	100% mortality	5	Zaroogian, 1978
American oyster (larva), *Crassostrea virginica*	12 days	50% mortality	46	Calabrese, et al. 1977
Black abalone, *Haliotis cracherodii*	4 days	Histopathological gill abnormalities	>32	Martin, et al. 1977
Red abalone, *Haliotis rufescens*	4 days	Histopathological gill abnormalities	>32	Martin, et al. 1977
Northern quahaug (larva), *Mercenaria mercenaria*	8-10 days	50% mortality	30	Calabrese, et al. 1977
Northern quahaug, *Mercenaria mercenaria*	77 days	53% mortality	25	Shuster & Pringle, 1968
Soft shelled clam, *Mya arenaria*	7 days	50% mortality (22°C)	35	Eisler, 1977
Soft shelled clam, *Mya arenaria*	7 days	50% mortality (4°)	>3,000	Eisler, 1977

Table 13. (Continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Mussel, Mytilus edulis	7 days	50% mortality	200	Scott & Major, 1972
Channeled whelk, Busycon canaliculatum	77 days	50% mortality	470	Betzer & Yevich, 1975
Mud snail, Nassarius obsoletus	3 days	Decrease in oxygen consumption	100	MacInnes & Thurberg, 1973
American lobster, Homarus americanus	13 days	50% mortality	56	McLeese, 1974
Coral-reef echinoid, Echinometra mathaei	4 days	Suppression of larval skeletal development	20	Heslinga, 1976
Sea urchin, Arbacia punctulata	--	58% decrease in sperm motility	300	Young & Nelson, 1974
Sea urchin, Paracentrotus lividus	4 days	Retardation of growth of pluteal larvae	10-20	Bougis, 1965
Mummichog, Fundulus heteroclitus	21 days	Histopathological lesions	<500	Gardner & La Roche, 1973
Mummichog, Fundulus heteroclitus	4 days	Enzyme inhibition	600	Jackim, 1973
Atlantic silversides, Menidia menidia	4 days	Histopathological lesions	<500	Gardner & La Roche, 1973
Summer flounder (embryo), Paralichthys dentatus	5 days	50% mortality	32	Cardin, et al. 1978
Summer flounder (embryo), Paralichthys dentatus	6 days	50% mortality	23	Cardin, et al. 1978
Plaice, Pleuronectes platessa	4 days	50% mortality	750	Saward, et al. 1975
Winter flounder, Pseudopleuronectes americanus	14 days	Histopathological lesions	180	Baker, 1969
Alga, Laminaria hyperboria	28 days	Growth decrease	50	Hopkins & Kain, 1971

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COPPER

Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

Copper is widespread in the earth's crust, and the extensive use of copper and its compounds by man since prehistoric times has added copper to the environment and the ecosystem in wide ranges of concentration.

From 1955 to 1958 the annual United States production of recoverable copper was about 900,000 metric tons. By 1975, the production had risen to 1,260,000 metric tons (D'Amico, 1958; U.S. Bur. Mines, 1976). The world trade in refined copper amounted to 2,271,150 metric tons in 1973 (World Metal Statistics, 1974).

Human exposure to copper can occur from water, food, and air, and through direct contact of tissues with items that contain copper. Copper is essential to animal life; consequently, abnormal levels of copper intake can range from levels so low as to induce a nutritional deficiency to levels so high as to be acutely toxic.

Ingestion from Water

Water can be a significant source of copper intake depending upon geographical location, the character of the water (i.e., whether it is soft or hard), the temperature of the water, and the degree of exposure to copper-containing conduits.

Schroeder, et al. (1966) place considerable emphasis on drinking water as a source of copper. They reported that the mean values of copper in human livers (56 cases) from Dallas, Denver, and Chicago varied from 410 to 456 μg/g of ash, and that the mean value from Miami was 578 μg/g of ash[1]. The municipal water supplies of these cities each provided relatively hard potable waters with measured hardness ranging from 75 to 125 mg/l. On the other hand, 143 livers from seven cities with relatively soft waters ranging from 10 to 60 mg/l had mean levels of copper varying from 665 to 816 μg/g of ash. Of the cases from softwater areas, 37.1 percent had hepatic copper of 700 or more μg/g of ash, compared with only 14.3 percent of the samples from the hardwater cities. Of the 56 individuals from three cities with the hardest water, only two showed such high values. Unfortunately no studies were made of cities with very hard water.

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[1] The values cannot readily be converted to total copper content present in liver on a wet weight basis since they were secured at autopsy. Information regarding the individuals from which samples came was minimal.

Schroeder, et al. (1966) suggested that the higher copper levels in residents of cities with soft water might be due to the ability of soft water to corrode copper pipes and fittings, thereby increasing the intake of soluble copper. Another explanation may lie in the ability of calcium or magnesium ions in hard water to suppress the intestinal absorption of copper.

Schroeder, et al. (1966) reported on the progressive increase of copper in water from brook to reservoir to hospital tap, and the considerable copper increment in soft water, compared with hard water, from private homes (see Table 1). The authors found that the daily increment of copper ingested from soft water may amount to 10 to 20 percent of dietary intake.

In contrast to Schroeder, et al. (1966), Hadjimarkos (1967) suggested that drinking water may be only a minor source of copper. He reported that the mean drinking water concentration of copper is 0.029 mg/l, which could mean a daily intake of 58 µg of copper in water, or 1 to 8 percent of total daily intake if food intake is 3,200 µg of copper per day.

It is probable that the difference in intakes estimated by Schroeder, et al. and Hadjimarkos reflects location. However, it is difficult to pinpoint local copper concentrations in drinking water sources, since the only readily available information on concentrations of copper in stream water is from areas of 10,000 square miles or greater (Kopp and Kroner, 1968; Thornton, et al. 1966).

TABLE 1

Copper in Water Flowing through Copper Pipes[a,b]

Item	µg/l.
Spring water, Brattleboro, Vermont, mountain	1.2[c]
Municipal water, soft, Brattleboro	
Brook, inlet to reservoir	16
Reservoir, lake	55
Water, main end	150
Hospital, at tap	
cold, running 30 min	170
hot, running 30 min	440
cold, standing 12 hr	550
cold, standing 24 hr	730
Spring water, soft, private houses, Brattleboro, Vermont, at tap	
No. 1 from spring, unpiped	2.8[c]
running 30 min	190
cold, standing 24 hr	1400
hot, standing 24 hr	1460[c]
No. 2	1240
No. 3	75
Well water, private houses, Windham County, at tap	
No. 4, hard	36
No. 5, hard	4.4[c]
No. 6, hard	40
No. 7, hard, at well	4[c]
at tap	36[c]
No. 8, soft	278

[a] Schroeder, et al. 1966.

[b] Water from the main was taken after it had passed through the treatment plant at the entrance to hospital supply system, from whence it ran through copper pipes. This water was chlorinated. Spring and well waters were untreated.

[c] By chemical method using diethyldithiocarbamate after evaporating 1 litre water.

Robinson, et al. (1973) in New Zealand have suggested that soft water used exclusively from the coldwater tap to make up daily beverages may add as much as 0.4 mg of copper per day per individual, but that if hot water from the same source is used for the same purposes, it would add at least 0.8 mg of copper per day to an individual's intake.

The average concentration of copper in the United States water systems is approximately 134 µg/l (U.S. Dep. Health, Edu. Welfare, 1970). The highest concentration reported was 8,350 µg/l; a little over 1 percent of the samples exceeded the drinking water standard of 1 mg/l.

The 1 mg/l copper standard was established not because of toxicosis but because of the taste which develops with higher levels of copper in the water. It is most commonly exceeded in soft water that is acid in nature; however, it is rare that the concentration of copper in drinking water is high enough to affect its taste or to produce toxicosis (McCabe, et al. 1970; Fed. Water Quality Adm., 1968). For this reason, regulatory agencies have not treated copper in public water supplies as a significant problem. In New York City, copper is intentionally added to the water supply to maintain a concentration of 0.059 mg/l in order to control algal growth (Klein, et al. 1974).

Prolonged contact of acid beverages with copper conduits, such as occurred in earlier drink dispensing machines, may produce sufficient copper concentration to cause acute copper toxicosis (see "Acute, Subacute, and Chronic Toxicity" section); however, because of taste problems, modern equipment does not contain copper conduits.

The national impact of a water-borne contribution of copper is difficult to detect, predict, or evaluate because information is either absent or irretrievable. The current trend for recycling waste (animal wastes, sewage solids, and liquids, channel dredging, and industrial waste) to the land offers very real possibilities that imbalances in organisms may unwittingly be created, because such wastes are commonly high in trace element concentration. These trace elements may directly alter crop production and indirectly affect the consumer (Patterson, 1971).

Another source of copper in water is the use of copper sulfate to control algae. Some idea of the distribution of copper sulfate may be gained from the work of Button, et al. (1977), who applied granular copper sulfate to the surface of Hoover Reservoir, Franklin County, Ohio. Soluble and particulate cupric copper concentrations at several depths were measured by atomic absorption spectrophotometry for four days after application. The soluble cupric copper concentration decreased to near baseline values in 2 to 6 hours when 0.2 or 0.4 gms of copper sulfate per square meter were added to the surface. Most of the copper sulfate was dissolved in the first 1.75 meters of water column, and only 2 percent of the total copper sulfate reached the depth of approximately 4.5 meters. A concentration of 0.4 gms of copper per square meter controlled a diatom bloom.

Ingestion from Foods

Levels of copper in various foods are given in Table 2. Some foods, such as crustaceans and shellfish (especially oysters), organ meats (especially lamb or beef liver), nuts, dried legumes, dried vine and stone fruits, and cocoa, are particularly rich in copper. The copper content of these items can range from 20 µg/g to as high as 400 µg/g (McCance and Widdowson, 1947; Schroeder, et al. 1966). On an "as-cooked and as-served" basis, calves' liver, oysters, and many species of fish and green vegetables have recently been classed as unusually good sources of copper, (more than 100 µg copper/100 kcal).

High levels of copper may also be found in swine because of the practice, common in the United Kingdom and elsewhere, of feeding to swine diets that are high (up to 250 µg/g) in copper in order to increase daily weight gain. Levels of copper in swine liver vary greatly depending on the copper content of the feed. A high copper diet fed continuously until slaughter may produce levels of up to 400 to 600 µg/g in the liver. However, swine will rapidly eliminate copper once it is removed from the diet. Sheep also accumulate copper in direct proportion to the level of copper in the diet, but they eliminate excess copper very poorly (NCR-42, 1974; Barber, et al. 1978). The National Research Council (1977) noted that the use of sheep or swine livers that are high in copper could result in excessive levels of copper, especially in baby foods where the actual amount of copper might exceed the copper requirements of very young children.

Copper in Foods (Wet Weight)[a]

Item	µg/g	µg/100 calories[b]
Sea food		
Clams, raw	3.33	694
Clams, fresh frozen	0.48	100
Oysters	137.05	27,410
Sardines, canned Portugese	1.12	38
Kipper snacks, Norway, canned	1.70	85
Anchovies, canned Portugese	0.81	27
Pan fish, dried, V.I.	0.58	49
Lobster, frozen	0.51	42
Shrimp, frozen	3.40	297
Mean, excluding oysters	1.49	167
Meat		
Beef liver	11.0	769
Beef kidney	0.42	34
Beef fat	0.83	21
Port kidney	5.30	441
Pork loin	3.90	130
Pork liver	3.72	260
Lamb kidney	0.95	96
Lamb chops	7.13	381
Chicken leg and wing	1.99	99
Mean	3.92	249
Dairy products		
Egg yolk	2.44	70
Egg white	1.70	460
Dried skimmed milk	2.09	63
Whole milk, dairy 1	0.26	40
Whole milk, dairy 2	0.12	18
Butter, salted	3.92	49
Mean	1.76	117
Vegetables		
Peas, green	0.45	70
Peas, split, green dry	12.30	410
Peas, green, V.I.	1.14	181
Peas, split, green, V.I.	2.25	75
Lentils	1.41	47
Yam, white V.I.	0.32	37
Yam, yellow, V.I.	0.41	47
Turnip, white	1.84	1022
Turnip greens	0.73	663

[a] Schroeder, et al. 1966

[b] Caloric values of foods from McCance, R.A. and, E.M.: Widdowson, The Chemical Composition of Foods. Chemical Publishing Co., Brooklyn, New York, 1947. V.I. indicates that the sample came from St. Thomas, Virgin Islands.

TABLE 2 (cont'd)
Copper in Foods

Item	µg/g	µg/100 calories[b]
Vegetables (cont'd)		
Beets	0.15	32
Carrots	3.42	1487
Tomato, V.I.	0.34	143
Pepper, green, No. 1	0.68	453
Pepper, green, No. 2	0.28	187
Pepper, green, V.I.	0.90	600
Pepper, hot, red, V.I.	0.56	-
Cucumber, No. 1	0.07	70
Cucumber, No. 2	0.47	470
Christofine, V.I.	0.18	257
Egg plant, V.I.	0.06	40
Asparagus	0.37	205
Celery	0.31	344
Cabbage	0.70	350
Parsley	0.20	-
Rhubarb	0.34	567
Mushrooms	0.65	929
Mean	1.17	362
Fruits		
Banana, V.I.	0.66	86
Papaya, V.I.	1.06	265
Coconut, V.I.	0.19	100
Coconut seed, V.I.	3.31	-
Apple, MacIntosh	1.39	278
Mean, excluding seed	0.82	182

TABLE 2 (cont'd)
Copper in Foods

Item	µg/g	µg/100 calories[b]
Grains and cereals		
Wheat seed	1.09	33
Wheat, whole	2.48	75
Wheat germ	0.15	-
Wheat head, chaff and stalk	0.14	-
Bread, white	0.19	8
Bread, whole wheat	0.63	25
Oats, whole	0.40	10
Corn, No. 1	0.46	13
Corn, No. 2	0.65	19
Rye, No. 1	0.92	27
Rye, No. 2	4.12	123
Rye, dry, flour	4.20	124
Benzene extract	10.82	-
Residue	1.87	-
Barley	3.83	106
Buckwheat	8.21	227
Rice, brown, U.S.	0.47	13
Rice, Japanese, polished	3.04	84
Bengal gram, India, 1	4.23	120
Bengal gram, India, 2	0.56	16
Grapenuts	14.95	415
Millet	2.34	67
Doughnut, cream filled	2.32	66
Mean, excluding grapenuts and extracts	2.02	58

TABLE 2 (cont'd)
Copper in Foods

Item	μg/g	μg/100 calories[b]
Oils and fats		
Lard, canned, 1	3.06	34
Lard, canned, 2	2.50	28
Lard, canned, 3	2.13	24
Lecithin, animal	26.38	-
Lecithin, egg	10.52	-
Cod liver oil, Norway	6.80	-
Castor oil, refined	1.70	-
Corn oil	2.21	25
Corn oil margarine	24.70	274
Cottonseed oil	1.26	14
Olive oil	3.20	36
Sunflower oil	5.44	60
Linseed oil, pressed	1.75	19
Peanut oil, pressed	0.83	9
Lecithin, vegetable, pure	5.31	-
Lecithin, soy, 90 percent pure	4.37	-
Lecithin, soy, refined	20.95	-
Mean, excluding lecithins	4.63	58
Nuts		
Hazelnuts	12.80	233
Peanuts	7.83	131
Walnuts	12.70	231
Brazil nut	23.82	370
Pecans	12.64	211
Almonds	14.11	234
Mean	14.82	235
Condiments, spices, etc.		
Garlic, fresh	3.15	-
Garlic powder	0.75	-
Mustard, dry	3.04	-
Pepper, black	20.73	-
Paprika	8.47	-
Chili powder	5.98	-
Thyme, ground	23.58	-
Bay leaves (laurel)	3.68	-
Cloves, whole	8.67	-
Ginger, ground	2.63	-
Ginger, root, V.I.	1.87	-
Caraway seeds	4.31	-
Vinegar, cider	0.76	-
Yeast, dry, active	17.79	-
Molasses	2.21	85
Sugar, refined	0.57	14
Mean	6.76	-

TABLE 2 (cont'd)
Copper in Foods

Item	µg/g	µg/100 calories[b]
Beverages		
Gin, domestic	0.03	1
Vermount, French	0.88	102
Vermouth, Italian	0.38	44
Whiskey, Scotch	0.35	14
Whiskey, Broubon	0.18	7
Brandy, California	0.45	18
Bitters, Angostura	0.75	-
Wine, domestic, red	0.28	33
Beer, canned	0.38	76
Cola	0.38	100
Grape juice	0.90	136
Orange drink, carbonated	0.20	43
Orange juice, packaged	0.89	234
Coffee, dry, ground	2.35	-
Coffee, infusion	0.22	-
Tea, infusion	0.31	-
Mean, excluding dry coffee	0.44	20
Miscellaneous		
Chocolate bar, Hershey	0.70	18
Ice cream, vanilla	0.29	15
Gelatin, Knox	3.87	148
Purina laboratory chow	15.61	-
Aspirin, Squibb	3.12	-
Saccharin	5.43	-

The poorer sources of copper are dairy products, white sugar, and honey, which rarely contain more than 0.5 µg copper/g. The non-leafy vegetables and most fresh fruits and refined cereals generally contain up to 2 µg/g. Cheese (except Emmental), milk, beef, mutton, and white and brown bread, and many breakfast cereals (unless they are fortified) are relatively poor sources of copper, i.e., they have less than 50 µg copper/100 kcal (World Health Organ. 1973).

The refining of cereals for human consumption results in significant losses of copper, although this loss is not so severe as it is for iron, manganese, and zinc. Levels of copper in wheat and wheat products are given in Tables 3 and 4.

Schroeder, et al. (1966) have suggested that since copper occurs widely in human foods, it is difficult to prepare a diet of natural foods which provides a daily copper intake of less than 2 mg, the level that is considered to be adequate for normal copper metabolism (Adelstein, et al. 1956).

Tompsett (1934) reported that the normal daily intake of copper from food appeared to be 2 to 2½ mg per day for human subjects. Daniels and Wright (1934) reported an average intake of 1.48 mg copper per day in young children, with a requirement of not less than 0.10 µg/kg of body weight per day.

TABLE 3

Mineral Content of Known Wheats, the Flours Milled from Them and the Products Prepared from the Flours[a,b]

Sample	Number of Samples	Moisture %	Ash %	Copper µg/g
Wheat, common hard	5	11.0	1.87 ± 0.10	5.1 ± 0.5
Flour, Baker's patent	5	13.9	0.49 ± 0.03	1.9 ± 0.2
Bread, sponge-dough	5	36.3	3.39 ± 0.19	2.3 ± 0.3
Bread, continuous-mix	5	35.3	3.42 ± 0.30	2.0 ± 0.2
Wheat, common soft	4	10.6	1.73 ± 0.17	4.5 ± 0.5
Flour, soft patent (cake)[c]	6	11.9	0.42 ± 0.03	1.6 ± 0.3
Cake	6	22.8	2.71 ± 0.11	0.8 ± 0.1
Flour, straight-grade[c]	5	11.4	0.50 ± 0.05	1.6 ± 0.2
Cracker	5	4.9	3.42 ± 0.50	1.6 ± 0.1
Flour, cut-off (cracker)	2	12.6	0.71 ± 0.04	2.6 ± 0.1
Cracker	2	4.5	3.09 ± 0.34	2.4 ± 0.1
Wheat, Durum	2	10.7	2.03 ± 0.01	4.8 ± 0.1
Semolina	2	14.7	0.83 ± 0.01	2.2 ± 0.1
Marcaroni	2	9.6	0.82 ± 0.01	2.5 ± 0.1

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[a] Zook, et al. 1970.

[b] Mean and standard deviation, dry weight basis.

[c] Includes two flours prepared by air classification.

TABLE 4

Mineral Content of Consumer Products Purchased in Ten Cities[a,b]

Product	Total Samples Collected No.	Producers Sampled Total No.	Producers Sampled Per City Range	Producers Sampled Model City No.	Moisture %	Ash %	Copper µg/g
Cereal-to-be-cooked	24	7	1-3	3	9.5	1.85 ± 0.07	5.3 ± 0.2
Shredded wheat	47	6	4-6	4	8.0	1.87 ± 0.12	6.1 ± 0.4
Wheat flakes	28	3	2-3	3	4.8	3.78 ± 0.17	4.7 ± 0.3
Bread, whole wheat	38	26	2-8	2	37.8	3.87 ± 0.12	5.1 ± 0.5
Bread, white							
Conventional dough	52	37	3-9	4	35.8	3.23 ± 0.12	2.1 ± 0.2
Continuous-mix	29	17	1-4	2	36.7	3.10 ± 0.13	2.3 ± 0.3
Rolls, hamburger	52	34	4-9	4	33.6	2.85 ± 0.08	2.5 ± 0.2
Doughnuts, cake	28	20	1-5	3	21.9	2.61 ± 0.20	1.7 ± 0.2
Biscuit mix	23	8	1-4	2	9.8	4.28 ± 0.26	1.6 ± 0.2
Flour, all-purpose	31	19	3-4	3	12.9	0.56 ± 0.03	1.8 ± 0.2

[a] Zook, et al. 1970.

[b] Mean and standard deviation, dry weight basis.

Most western style diets supply adults with 2 to 4 mg of copper per day. This is evident from studies in England, New Zealand, and the United States. Lower estimates have been made for certain Dutch and poorer Scottish diets, while Indian adults consuming rice and wheat diets have been shown to ingest from 4.5 to 5.8 mg of copper per day (Schroeder, et al. 1966).

Scheinberg (1961) has contended that most adult diets supply a substantial excess of copper. Klevay, on the other hand, has suggested on the basis of recent food analyses that the copper content may be less than earlier analyses indicated and has cautioned that United States diets may not be adequate to provide 2 mg of copper per day. (Klevay, 1977; Klevay, et al. 1977).

Dr. Walter Mertz in a personal communication reported that in 1978 the analysis of diets of more than 20 individuals employed at the Institute of Nutrition of the U.S. Department of Agriculture, Beltsville, Md., showed that only two approached an intake of 2 mg of copper per day. The diets of these individuals included soft drinks, water, and snacks, suggesting that food subjected to modern processing and preparation methods may be much lower in copper than was supposed based on earlier analyses, and that many individuals eating these foods may be receiving considerably less than the 2 mg of copper per day.

Engel, et al. (1967) conducted studies on young girls which indicated that 2 µg copper/g of diet was adequate for good nutrition. Petering, et al. (1971) mention that the copper content of hair appears to be related to the age of the individual and suggest that the need for copper may differ between the sexes.

Because of the essentiality of copper, the copper balance in newborn infants has been examined (Cavell and Widdowson, 1964). It was noted that breast milk ranged from 0.051 mg/100 ml and that total copper intakes of the babies ranged from 0.065 to 0.1 mg/kg per day. In the first week of life, some infants excreted more copper than was contained in the milk which they consumed. Of 16 babies, 14 were in negative balance.

As a general statement it would appear that, at least in the United States, there is a greater risk of inadequate copper intake than of an excess above requirements.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. Since BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey, the relative consumption of the four major groups can be calculated.

A bioconcentration factor of zero was reported for copper in the muscle of bluegill sunfish (Benoit, 1975). Since no data are available for saltwater fish or decapods, the same value will be used. Data are available for several species of saltwater molluscs:

Species	BCF	Reference
Bay scallop, *Argopecten irradians*	3,310	Zaroogian, 1978
Bay scallop *Argopecten irradians*	4,155	Zaroogian, 1978
American oyster, *Crassostrea virginica*	28,208	Shuster & Pringle, 1969
American oyster, *Crassostrea virginica*	20,688	Shuster & Pringle, 1969
Northern quahaug, *Mercenaria mercenaria*	88	Shuster & Pringle, 1968
Soft shelled clam, *Mya arenaria*	3,300	Shuster & Pringle, 1968
Mussel, *Mytilus edulis*	208	Zaroogian, 1978
Mussel, *Mytilus edulis*	108	Zaroogian, 1978
Mussel, *Mytilus edulis*	90	Phillips, 1976
Mussel, *Mytilus galloprovincialis*	800	Majori & Petronio, 1973

The geometric means for scallops, oysters, clams, and mussels are 3,708, 24,157, 539, and 200, respectively, and the overall mean is 290.

Group	Consumption (Percent)	Bioconcentration factor
Freshwater fishes	12	0
Saltwater fishes	61	0
Saltwater molluscs	9	290
Saltwater decapods	18	0

Using the data for consumption and BCF for each of these groups, the weighted average BCF is 26 for consumed fish and shellfish.

Inhalation

The principal source of elevated copper levels in air is copper dust generated by copper-processing industrial operations. However, since the economic value of copper encourages its capture from industrial processes, extraneous emissions are reduced. Other possible sources of copper in air may be tobacco smoke and stack emissions of coal-burning power plants.

Copper has not been considered a particularly hazardous industrial substance because the conditions that would produce excessive concentrations of copper dust or mist in a particle size that could be absorbed and generate toxic effects are apparently quite rare. Investigations of Chilean copper miners have shown that liver and serum concentrations of copper are normal, despite years of exposure to copper sulfide and copper oxide dust, both of which are insoluble (Scheinberg and Sternlieb, 1969). However, workers can be exposed to excess concentrations of copper in any of its forms, and when this does occur undesirable health effects can result. Metal fumes, a 24 to 28-hour illness characterized by chills, fever, aching muscles, dryness in the mouth and throat, and headache, has been noted where workers are exposed within closed areas to the welding of copper structures (McCord, 1960).

Special care should be taken to avoid conditions where copper or a copper compound dust is a problem (Cohen, 1974). The U.S. Occupational Safety and Health Administration (OSHA) has adopted standards of exposure to air-borne copper at work. The time-weighted average for 8-hour daily exposure to copper dust is limited to 1 mg/m^3 of air. The standard for copper fume was changed in 1975 to 0.2 mg/m^3 (Gleason, 1968; Nat. Res. Counc. 1977).

In 1966, a National Air Sampling Network survey showed that the airborne copper concentrations were 0.01 and 0.257 $\mu g/m^3$ in rural and urban communities respectively (Nat. Air Pollut. Control Admin. 1968). Even near copper smelters, where high levels (1 to 2 $\mu g/m^3$) are reached the dose of metal that would be acquired through inhalation of ambient air would comprise only about 1 percent of the total normal daily intake (Schroeder, 1970).

Generally speaking, inhalation of copper or copper compounds is of minor significance compared to other sources, e.g., copper in foods, drinking water, and other fluids, and application of copper to tissues for medical purposes.

Dermal

Copper toxicity has resulted from the application of copper salts to large areas of burned skin or from introduction of copper into the circulation during hemodialysis. The source of the copper in hemodialysis may be the membranes fabricated with copper, the copper tubing, or heating coils of the equipment. Copper stopcocks in circuits can also cause potentially hazardous infusions of copper (Holtzman, et al. 1966; Lyle, et al. 1976).

Studies with monkeys indicated that copper used as dental fillings and placed in cavities in the deciduous teeth of the monkey caused more severe pulp damage than any of the other materials studied. This is additional evidence that tissues exposed directly to copper or copper salts will suffer adverse effects due to the direct absorption of the copper by the tissues (Mjor, et al. 1977).

Recent papers from Australia (Walker, 1977; Walker, et al. 1977) suggest the possibility of copper absorption through the skin as a result of perspiration action on the copper bracelet, sometimes worn as treatment for arthritis, although the therapeutic value of this has little support.

Concern has been directed toward the absorption of copper as a result of the use of the intrauterine device (IUD) as a contraceptive measure (National Research Council, 1977). Analysis of IUDs that have been in utero for months to years shows that about 25 to 30 mg of copper are lost each year. Some of the metal is excreted with endometrial secretions. Experimental evidence to date does not indicate that use of an IUD results in harmful accumulations of copper. (See "Absorption" section for additional information.)

PHARMACOKINETICS[1]

Absorption

Radioactive studies provide the basis for the conclusions that most absorption in man takes place in the stomach and the duodenum. Copper absorption appears to be regulated by the intestinal mucosa, and maximum copper levels occur in the blood serum within one to three hours after oral intake.

Much of the information on copper absorption in humans has come from studies of patients with Wilson's disease. Studies conducted with these patients using radioactive copper indicate that about one-half of the copper in the diet is not absorbed but is excreted directly into the feces. The average absorption in these individuals has been reported to be approximately 40 percent (Sternlieb, 1967; Strickland, et al. 1972a). Investigations by Cartwright and Wintrobe

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[1] Acknowledgement is made of the courtesy of the late Dr. Karl E. Mason and Dr. Walter Mertz who allowed the author to read their manuscript, Conspectus on Copper, to be published in the Journal of Nutrition.

(1964a) indicated that the daily intake of copper in Wilson's disease patients was 2 to 5 mg, of which 0.6 to 1.6 mg were absorbed, 0.5 to 1.2 mg were excreted in the bile, 0.1 to 0.3 mg passed directly into the bowel, and 0.01 to 0.06 mg appeared in the urine.

Information from these studies indicates that absorbed copper is rapidly transported to blood serum and taken up by the liver, from which it is released and incorporated into ceruloplasmin. Any copper remaining in the serum is attached to albumin or amino acids or is used to maintain erythrocyte copper levels (Weber, et al. 1969; Bearn and Kunkel, 1954, 1955; Beckner, et al. 1969; Bush, et al. 1955; Jensen and Kamin, 1957).

Estimates of the amount of the copper that is actually absorbed by normal individuals vary considerably and must be considered inconclusive. The values obtained have ranged from as low as 15 percent to as high as 97 percent (Weber, et al. 1969), although it seems probable that subjects giving these extreme values were not in a steady state. These values are confounded by the lack of accurate information regarding the excretion of copper in its various forms by way of the biliary system. Even less information is available regarding the reabsorption of copper or copper compounds from the intestine after they have been excreted in the bile.

Most of the values that have been obtained with normal subjects suggest that 40 to 60 percent of the dietary copper is absorbed (Van Ravensteyn, 1944; Cartwright and Wintrobe, 1964a; Bush, et al. 1955; Matthews, 1954; Weber, et al. 1969; Strickland, et al. 1972a; Strickland, et al. 1972b; Sternlieb, 1967).

Animal studies have shown that copper is absorbed by at least two mechanisms, an energy-dependent mechanism and an enzymatic mechanism (Crampton, et al. 1965), and that many factors may interfere with copper absorption, including competition for binding sites as with zinc, interactions with molybdenum and with sulphates, chelation with phytates, and the influence of ascorbic acid. Ascorbic acid will aggravate copper deficiency by decreasing copper absorption. In cases of excess copper intake, ascorbic acid can reduce the toxic effects (Gipp, et al. 1974; Hunt, et al. 1970; Voelker and Carlton, 1969).

Studies with laboratory animals have shown that once copper enters the epithelial cells, it is taken up by a cellular protein similar to metallothionein which occurs in liver (Evans, et al. 1973; Evans, 1973; Starcher, 1969). Absorbed copper is bound to albumin and transported in the plasma. Approximately 80 percent of the absorbed copper is bound in the liver to metallothionein. The remaining copper is incorporated into compounds such as cytochrome-c-oxidase or is sequestered by lysosomes (Bearn and Kunkel, 1954, 1955). Little information is available concerning absorption of copper into the lymphatics, although in pathological conditions this may be signficiant (Trip, et al. 1969).

Several studies have been conducted on humans and laboratory animals concerning absorption of copper as a result of the use of copper intrauterine devices (IUD's). Studies with the IUD in rats have suggested that as much as 10 to 20 mg of copper may be absorbed (Oreke, et al. 1972). This amount, which is small compared to the dietary copper usually ingested, may or may not be metabolized and excreted by the same homeostatic mechanisms that operate with ingested copper. If an IUD were used for many decades and the absorbed copper were retained, it would result in amounts of copper similar to those retained from dietary copper by patients with Wilson's disease. Such levels could result in chronic toxicosis.

Japanese investigators (Okuyuma, et al. 1977) have compared effects of using the IUD with copper and the IUD without copper in two groups of women, using a third group as controls. Pregnant women with an IUD in place were also examined. No significant difference was found in the endometrial copper levels in the three groups. There was a tendency toward an increase above controls in the endometrial level of copper during the secretory phase in those women using the IUD with or without copper. No significant difference was found between women who had used an IUD more than 13 months and those who had used it less than 13 months. The copper content of the chorion and the decidua of the pregnant women with IUD's in place did not differ from the levels noted in pregnant women without IUD's. Apparently, the long-term use of copper-containing IUDs did not lead to an accumulation of copper in the uterus.

Tamaya, et al. (1978) have studied the effect of the copper IUD on the histology of the endometrium in the proliferative and the secretory phases of women. Their results indicate that the copper IUD affected the secretory endometrium but not the proliferative endometrium.

In another study, Israeli women with the Latex Leaf IUD which contains both copper and zinc showed increased levels of both metals if they had had low serum levels of copper and zinc before insertion. However, their copper and zinc levels did not exceed the upper limits of normal values. No significant statistical difference was found between the serum levels of copper before and after insertion of the IUD.

It has been suggested that diabetic women may respond differently from normal healthy women to the use of a copper IUD. In 11 diabetics, the presence of a copper IUD did not increase the fibrolytic activity in the endometrium, although such an effect was observed in non-diabetics. Since there is evidence that enhancement of the endometrial fibrolytic activity prevents adhesion and implantation of ova, the results may explain the report of less reliable contraceptive effect of the IUD in diabetic women (Larsson, et al. 1977).

A number of studies of the effect of copper upon fertility in animals have incidentally measured copper in tissues. Studies of copper beads in rabbits (Quijada, et al. 1978), copper wires inserted into the vas deferens of male rats

(Kartar and Chowdhury, 1977), and copper IUDs in rats have all suggested that copper does have some influence on hormone secretion and tissue copper levels in the reproductive tract; however, these experiments do not present any evidence for accumulation of copper as a result of the use of IUDs (Murakimi, et al. 1978).

Distribution

The amount and distribution of copper in body tissues varies with sex, age, and the amount of copper in the diet. Copper content of fat-free tissues of most animals ranges upward from about 2 µg/g. The highest concentrations of copper in both animal and human tissues are found in the liver and the brain, with lesser amounts in the heart, the spleen, the kidneys, and blood (Cartwright and Wintrobe, 1964a,b; Smith, 1967; Schroeder, et al. 1966). Some tissues are very high in copper, e.g., the iris and the choroid of the eye which may contain as much as 100 µg/gm (Bowness and Morton, 1952; Bowness, et al. 1952).

Estimates of the total amount of copper in a 70-kilogram man have ranged from 70 to 120 mg. Approximately one-third of body copper is found in the liver and the brain, one-third is found in the musculature, and the remaining one-third is dispersed in other tissues. It has been estimated that, on the average, about 15 percent of the total body copper is contained in the liver (Tipton and Cook, 1963; Sumino, et al. 1975; Sass-Kortsak and Bern, 1978). The relatively high percentage of liver copper is related to the liver's function as a storage organ for copper and as the only site for the synthesis and release of ceruloplasmin, the most abundant copper protein in the blood.

In the brain, the striatum and both components of the cortex (gray matter) have the highest copper content, with the cerebellum (white matter) being the lowest (Hui, et al. 1977; Cumings, 1948; Earl, 1961). The brain appears to be the only tissue in which there is a consistent increase in copper content with age. Other tissues appear to be under a homeostatic control.

Copper levels in hair vary widely with respect to age, sex, and other factors, and therefore have little meaningfulness in evaluating copper levels in man (Underwood, 1977). However, Jacob, et al. (1978) have suggested that the copper in hair may be useful in evaluating the total liver content of copper. Engel, et al. (1967) surveyed over 180 adolescent girls in the 6th to 8th grades for dietary intake and nutritional status. They found that the mean concentration of copper in hair samples was 31 ± 23 µg/g. No significant difference was found between girls who had experienced menarche and those who had not.

Levels of copper in the blood of normal adults average 103 µg/100 ml of blood. The amount of copper in blood serum can range widely from 5 µg/100 ml to 130 µg/100 ml. In practically all species, copper deficiency is first manifested by a slow depletion of body copper stores, including the blood plasma, eventually resulting in a severe anemia identical to that caused by iron deficiency (Cartwright, et al. 1956).

Both the plasma and the erythrocyte have two pools of copper, a labile pool and a stable pool, which contain approximately 40 and 60 percent respectively, of the copper in the blood (Bush, et al. 1956). Ceruloplasmin represents the serum stable pool. There appears to be little or no interchange between ceruloplasmin copper and other forms of copper in the blood stream (Sternlieb, et al. 1961). Mondorf, et al. (1971) indicate that the blood contains an average of 30 µg of ceruloplasmin/100 ml of blood. This is in reasonable accord with accepted levels of copper in the blood of normal adults (approximately 103 µg total copper/100 ml of blood. White blood cells contain a small amount of copper, about one-fourth the concentration in erythrocytes (Cartwright, 1950).

The distribution of copper in the fetus and in infants is quite different from that in the adult. The percentage of copper in the body increases progressively during fetal life (Shaw, 1973). Chez, et al. (1978) found that concentrations of copper in amniotic fluid increased between the 26th and 33rd weeks of pregnancy, but that there did not appear to be a correlation between maternal and fetal copper concentrations.

At birth, the liver and spleen contain about one-half the copper of the whole body (Widdowson and Spray, 1951). A newborn infant contains about 4 mg/kg as compared to approximately 1.4 mg/kg in the 70-kilogram man (Widdowson and Dickerson, 1964). The liver of the newborn has approximately

6 to 10 times the amount of copper in the liver of an adult man on a per gram basis (Bruckmann and Zondek, 1939; Nusbaum and Zettner, 1973; Widdowson, et al. 1951).

The concentration of copper in the serum of newborn infants is significantly lower than in 6- to 12-year-old healthy children, but by 5 months of age the serum concentration of copper is approximately the same as in older children. There is no difference between copper levels in male and female infants, although breast-fed infants seem to have somewhat higher copper levels by 1 month than bottle-fed infants (Ohtake, 1977). The liver copper content of the fetus is several times higher than maternal liver copper (Seeling, et al. 1977).

Metabolism

The copper content of red blood cells remains remarkedly constant, but the plasma copper is subject to striking changes associated with the synthesis and release of ceruloplasmin, the most abundant copper protein (Gubler, et al. 1953; Lahey, et al. 1953).

Some 20 mammalian copper proteins have been isolated, but at least three are identical and others have more than one name. Most of this information has come from animal studies, and its applicability to humans is uncertain. Evans (1973) and others have reviewed this subject (Mann and Keilin, 1938; Osborn, et al. 1963; Morell, et al. 1961; Sternlieb, et al. 1962).

Copper plasma levels during pregnancy may be two to three times the normal nonpregnant level. This is almost entirely due to the increased synthesis of ceruloplasmin (Henkin, et al. 1971; Markowitz, et al. 1955; Scheinberg, et al. 1954). The source of this copper appears to be the maternal liver. The increase in maternal plasma copper levels appears to be associated with estrogen, since either sex receiving estrogen shows an increase in copper level of the plasma (Elsner and Hornykiewicz, 1954; Gault, et al. 1966; Humoller, et al. 1960; Russ and Raymunt, 1956).

The use of oral contraceptives causes a marked increase in serum copper levels which may be greater than those observed during pregnancy (Oster and Salgo, 1977; Smith and Brown, 1976; Tatum, 1974).

Infant levels of serum copper are low at birth but promptly increase due to the synthesis of ceruloplasmin by the infant's liver (Henkin, et al. 1973; Schorr, et al. 1958).

There are two inherited diseases which represent abnormal copper metabolism, Menkes' disease and Wilson's disease. Menkes' disease is a progressive brain disease caused by an inherited sex-linked recessive trait. It is often referred to as the "kinky hair" disease or "steely hair" disease (Danks, et al. 1972). The primary defect of Menkes' disease appears to be a diminished ability to transfer copper across the absorptive cells of the intestinal mucosa (Danks, et al. 1972, 1973). The general symptoms of the disease are similar to those observed in animals suffering from copper deficiency (Oakes, et al. 1976). The prospects for more effective therapeutic measures as a result of early diagnosis appear to be limited.

The second abnormal disease associated with copper, Wilson's disease, which has also been designated "hepatolenticular degeneration," is caused by an autosomal recessive trait (Bearn, 1953). The disease is actually a copper toxicosis with abnormally high levels of copper in the liver and brain (Cumings, 1948). Symptoms include increased urinary excretion of copper (Spillane, et al. 1952; Porter, 1951); low serum copper levels due to low ceruloplasmin (Scheinberg and Gitlin, 1952); decreased intestinal excretion of copper; and occurrence of Kayser-Fleischer rings due to excessive accumulation of copper around the cornea. If therapy with D-penicillamine is instituted during the early phases of Wilson's disease, it can assure a normal life expectancy, especially when accompanied by a low-copper diet (Deiss, et al. 1971; Sternlieb and Scheinberg, 1964, 1968; Walshe, 1956).

Other abnormalities of copper metabolism are primarily associated with low levels of copper. Hypocupremia, which is defined as 80 µg or less of copper/100 ml (Cartwright and Wintrobe, 1964a), usually refers to a low ceruloplasmin level. In most cases it is probably due to a dietary deficiency of copper or to a failure to synthesize the apoenzyme of ceruloplasmin (Kleinbaum, 1963). Hypocupremia can also result from malabsorption that occurs during a small bowel disease (Sternlieb and Janowitz, 1964).

Hypercupremia, abnormally high levels of copper, occurs with a number of neoplasms (Delves, et al. 1973; Herring, et al. 1960; Goodman, et al. 1967; Janes, et al. 1972). Elevated serum copper levels occur in psoriasis (Kekki, et al. 1966; Molokhia and Portnoy, 1970).

It is well recognized that copper is necessary for the utilization of iron. Much of this work has been done in animals, and the subject is well covered by Underwood (1977). It appears that ceruloplasmin is essential for the movement of iron from cells to plasma (Osaki, et al. 1966). Reticulocytes from copper-deficient animals can neither pick up iron from transferrin normally nor synthesize heme from ferric iron and protoporphyrin at the normal rate (Williams, et al. 1973).

The ratio of copper to other dietary components, e.g. zinc and iron, may be almost as important as the actual level of copper in the diet in influencing the metabolic response of mammalian species (Smith and Larson, 1946). The cardiovascular disorder "falling disease", reported by Bennetts, et al. (1942), is associated with a copper deficiency in cattle. Similar conditions have been observed in pigs and chickens (O'Dell, et al. 1961; Shields, et al. 1961). In this disorder the elastic tissue of major blood vessels is deranged, markedly reducing the tensile strength of the aorta. This appears to be associated with a biochemical lesion, the reduced activity of lysyl oxidase, a copper-requiring enzyme necessary for elastic tissue formation and maintenance (Hill, et al. 1967).

Evans has discussed the metabolic disorders of copper metabolism including nutritional disorders, inborn order errors of proper homeostasis, and disorders due to the lack of copper-requiring enzymes (Evans, 1977).

Particular attention has been given to the role of copper as associated with cardiovascular diseases (Vallee, 1952; Adelstein, et al. 1956). More recently there has been considerable interest in the role of copper and its ratio to zinc as a factor in the level of cholesterol and cholesterol metabolism as it may relate to ischemic heart disease (Klevay, 1977). It has been suggested that a low copper - high zinc ratio may result in an increased level of cholesterol, particularly that part of the blood cholesterol in the serum low density lipoprotein which has been associated with increased susceptibility to ischemic heart disease (Allen and Klevay, 1978a,b; Petering, 1974; Lei, 1978; Klevay, et al. 1977). In a different context, Harman (1970) has suggested that copper in the diet in excess of needs may result in free radicals that cause adverse effects in the cardiovascular system.

Excretion

It has been noted that perhaps 40 percent of dietary copper is actually absorbed (Cartwright and Wintrobe, 1964a). These estimates are largely based on the difference between oral intake and fecal excretion. Urinary excretion of copper plays a very minor role. The fecal excretion represents unabsorbed dietary copper and the copper that is excreted by the biliary tract, the salivary glands and the gastric and intestinal mucosae (Gollan and Deller, 1973). It should be noted that some of the excreted copper is reabsorbed in the course of its movement down the intestinal tract. Some loss of copper may occur by way of sweat and in the female menses.

One of the principal routes of excretion is by way of the bile; however, because of the difficulty in studying biliary excretion in normal subjects, the evidence for quantitative values of copper excretion by this route is fragmentary. Cartwright and Wintrobe (1964a) suggest that 0.5 to 1.2 mg per day is excreted in the bile. This is in reasonable accord with the report (Frommer, 1974) that excretion was approximately 1.2 mg per day in ten control subjects. It is possible that very little of the copper excreted in the bile is reabsorbed (Lewis, 1973).

Some copper (approximately 0.38 to 0.47 mg per day) is excreted in the saliva, but there is little evidence as to whether this copper is or is not absorbed in the intestine (DeJorge, et al. 1964).

It is possible that the gastric secretion of copper approximates 1 mg of copper per day, but there is very little published information on this subject (Gollan, 1975).

The amount of copper excreted in the urine is small. Estimates range from 10 to 60 μg per day and average 18 μg per day (Cartwright and Wintrobe, 1964a; Zak, 1958). It is possible, of course, that copper may be reabsorbed from the kidney tubules (Davidson, et al. 1974).

Studies in New Zealand conducted on young women with a copper intake of 1.8 to 2.09 mg per day showed an excretion in the feces of between 65 and 94 percent of the intake. The urinary excretion amounted to 1.7 to 2.2 percent of the intake (Robinson, et al. 1973).

Under some conditions a considerable amount of copper may be lost through sweat, perhaps as much as 1.6 mg of copper per day or about 45 percent of the total dietary intake (Consolazio, et al. 1964).

There is very little information on the loss of copper by way of the menstrual flow but an average value of 0.11 ± 0.07 mg per period seems reasonable (Ohlson and Daum, 1935; Leverton and Binkley, 1944).

Sternlieb, et al. (1973) note that 0.5 to 1.0 mg of copper is catabolized daily by the adult liver and about 30 mg of ceruloplasmin, which contains 0.3 percent copper, is excreted into the intestine (Waldmann, et al. 1967). The copper excreted into the intestine in the bile may not be readily available for reabsorption because it is bound to protein; the copper found in the feces seems to come from various secretions, as well as the copper which is not absorbed from food (Gollan and Deller, 1973).

In summary it may be said that most copper is excreted by way of the biliary system with additional amounts in sweat, urine, saliva, gastric and intestinal mucosae, and in women in the menses.

Examination of the pharmokinetic data points up the fact that the biological half-life of copper is very short. This provides significant protection against accumulations of copper even with intakes considerably above levels considered adequate.

EFFECTS

Acute, Sub-Acute, and Chronic Toxicity

Copper toxicity produces a metallic taste in the mouth, nausea, vomiting, epigastric pain, diarrhea, and, depending on the severity, jaundice, hemolysis, hemoglobinuria, hematuria, and oliguria. The stool and saliva may appear green or blue. In severe cases anuria, hypotension, and coma can occur.

Toxic levels of copper ingested are promptly absorbed from the upper gut and the copper level in the blood is rapidly increased, primarily because of an accumulation in the blood cells. Hemolysis occurs at high copper levels. A high level in the blood can also result from absorption through the denuded skin, as when applied to burns, because of dialysis procedures or because of exchange transfusions. The hemolysis is due to the sudden release of copper into the blood stream from the liver which has been damaged by an increasing load of copper and is unable to utilize the copper in the synthesis of ceruloplasmin, which in turn can be excreted by way of the biliary system (Chuttani, et al. 1965; Bremmer, 1974; Cohen, 1974; Deiss, et al. 1970; Roberts, 1956; Bloomfield, et al. 1971; Ivanovich, et. al. 1969; Bloomfield, 1969).

Chatterji and Ganguly (1950) describe a non-fatal type of copper poisoning in which the symptoms are laryngitis, bronchitis, intestinal colic with catarrh, diarrhea, general emaciation, and anemia.

Burch, et al. (1975) have estimated that the chronic toxic intake level of inorganic copper for an adult man is 10 to 15 mg per dose. The vomiting and diarrhea induced by ingesting small quantities of ionic copper generally protect the patient from the serious systemic toxic effects which include hemolysis, hepatic necrosis, gastrointestinal bleeding, oliguria, azotemia, hemoglobinuria, hematuria, proteinuria, hypotension, tachycardia, convulsions or death (Chuttani, et al. 1965; Davenport, 1953).

Because most of the information about acute copper toxicity in humans has come from attempts at suicide or from the accidental intake of large quantities of copper salts, the information about the changes occurring with acute toxicity are meager.

Acute copper poisoning does occur in man when several grams of copper sulfate are eaten with acidic food or beverages such as vinegar, carbonated beverages, or citrus juices (Walsh, et al. 1977). Some cases of acute poisoning have occurred when tablets containing copper sulfate were given to children (Forbes, 1947).

When carbonated water remains in copper check valves or drink-dispensing machines overnight, the copper content of the first drink of the day may be increased enough to cause a metallic taste, nausea, vomiting, epigastric burning, and diarrhea (Hooper and Adams, 1958). Drinks that are stored in copper-lined cocktail shakers or vessels can have the same effect (Pennsylvania Morbidity and Mortality Weekly Reports, 1975; McMullen, 1971).

Salmon and Wright (1971) have reported the possibility of chronic copper poisoning as a result of water moving through copper pipes. They document a case in which a family moved into a house in North London with a hot water system entirely composed of copper. The water was stored in a 40-gallon copper tank which reached a temperature of 93° Celsius at night. The family used hot water for all cooking and beverages. After two months, the electric kettle was coated inside with a thick green film of the copper complex. The child in the family was admitted to the hospital after five weeks of behavior change, diarrhea, and progressive marasmus. When first seen the clinical picture was that of "pink" disease with prostration, misery, red extremities, hypotonia, photophobia, and peripheral edema. The liver was palpable for 2 cm below the costal margin. The serum copper level was 286 µg/100 ml, compared to a normal range of 164 ± 70 µg/100 ml. Analysis found 35 ug copper/100 ml of cold water in the home, and 79 µg/100 ml hot water. Cold and hot water levels in the hospital were 4 and 30 µg/100 ml respectively, and in North London the values were 8 and 16 µg/100 ml.

Walker-Smith and Blomfield (1973) found that a child showing symptoms of Wilson's disease had in fact drunk water with a very high copper level (675 µg/100 ml). Therefore, they suggest that individuals with suspected cases of Wilson's disease should have the copper content of their drinking water investigated.

Eden and Green report on a male infant who received high levels of copper, resulting in chronic copper poisoning from contaminated water ingested over a period of 3 months. Treated with D-penicilliamine and prednisolone, the infant made a slow recovery (Eden and Green, 1940).

In general, however, the problems associated with high levels of copper in drinking water are more of less controlled because of taste (since high levels of copper in water produce a metallic taste) or because of cosmetic considerations (since water with high copper content develops a surface scum due to the formation of insoluble copper compounds).

Chronic toxicity has been studied in animals, and there appears to be a wide variation in the tolerance of different species for high levels of copper in the diet. Sheep are very susceptible to high copper intakes, whereas rats have been shown to be very resistant to the development of copper toxicity.

Swine will develop copper poisoning at levels of 250 µg of copper/g of diet unless zinc and iron levels are increased. Suttle and Mills (1966) have studied dietary copper levels ranging up to 750 µg/g in the diet of swine. Toxicosis does develop with hypochromic microcytic anemia, jaundice, and marked increases in the liver and serum copper levels as well as serum aspartate amino transferase. These signs of copper toxicosis in swine can be eliminated by including an additional 150 µg of zinc and of iron/g of diets containing up to 450 µg of copper/g; the addition of even more zinc and iron, 500 to 750 µg/g, will overcome the effects of 750 µg of copper/g of diet.

Chronic oral intake of copper acetate in swine and rats can produce a condition comparable to hepatic hemosiderosis in man (Mallory and Parker, 1931a). Some question exists as to whether hemosiderosis in man is a result of copper toxicity, because people consuming comparatively high levels of copper do not develop this condition regularly.

Sheep are quite susceptible to high levels of copper in the diet. Levels of 35 µg/g of feed have resulted in toxicity when fed over a period of 9 months to 1 year (Fontenot, et al. 1972). Cattle are much more resistant to copper in the diet; 2 grams of copper sulfate given daily did not produce toxic reactions (Cunningham, 1931).

It is well known that with ruminant animals, molybdenum and sulfate interact with the copper. Copper toxicity is counteracted by inclusion of molybdenum and sulfate in the diet of ruminants (Dick, 1953; Kline, et al. 1971; Wahal, et al. 1965).

Synergism and Antagonism

There is some evidence that copper may increase the mutagenic activity of other compounds. Using strain TA-100 of Salmonella typhimurium, Omura, et al. (1978) studied the mutagenic actions of triose reductone and ascorbic acid. They found that the addition of the copper to triose reductone at a ratio of 1:1000 lowered the most active concentration of the triose reductone to 1 mM from 2.5 to 5 mM.

Another enediol reductone, asborbic acid, had no detectable mutagenic action by itself, but a freshly mixed solution of 5 mM of ascorbic acid and 1 or 5 µM of cupric copper had an effective mutagenic action. Ascorbyl-3-phosphate had no mutagenic function even in the presence of cupric copper. The investigators suggested that it was the enediol structure in the reductones that was the essential for mutagenicity.

In the "Acute, Subacute, and Chronic Toxicity" section, it was pointed out that the dietary levels of zinc and iron are as important as the level of copper in determining the toxic level of copper.

Teratogenicity

There is very little evidence in the literature to suggest that copper has a teratogenic effect in either animals or humans.

Mutagenicity

No data were found to suggest that copper itself has a mutagenic effect in either animals or humans; however, one report exists suggesting that copper may increase the mutagenic activity of other compounds (see "Interactions, Including Synergism and Antagonism" section).

Carcinogenicity

There is very little evidence in the literature to suggest that copper has a carcinogenic effect in either animals or humans. Pimental and Marques (1969) noted that vineyard workers in France, Portugal, and southern Italy exposed to copper sulfate sprays mixed with lime to control mildew developed granulomas and malignant tumors in their livers and lungs (Pimental and Menezes, 1975; Villar, 1974). Because of the route of exposure, quantitative estimates are, at best, speculative.

It has been noted earlier that the conditions in industry that would produce excessive concentrations of copper as a dust or a mist with particle sizes that would result in toxic effects if the copper were absorbed are apparently quite rare. Some investigators have suggested that lung cancer, which has been present with increased frequency in workers in copper smelters, is actually due to the arsenic trioxide in the dust and that the copper itself did not play any etiologic role in the development of the cancer (Kuratsune, et al. 1974; Lee and Fraumeni, 1969; Milham and Strong, 1974; Tokudome and Kuratsune, 1976).

Some studies have reported that, with the development of various tumors, the copper content of both blood and the tumor tissue is likely to increase, although this is not always the case (Pedrero, 1951). However, when an increase occurs, it appears to be more a result of an inflammatory reponse or stress than any direct causative relationship.

Czech workers have noted that the high copper content of melanomas is probably due to the presence of the copper-containing enzyme tyrosinase.

Polish workers (Legutko, 1977) have suggested that the copper level of the serum is a particularly sensitive indicator of the clinical condition and effectiveness of treatment of lymphoblastic leukemia in children, but again no particular relationship to the development of the leukemia is indicated.

Russian scientists (Bezruchko, 1976) have also studied the copper and ceruloplasmin in patients with cancer and noted that the levels of both ceruloplasmin and copper were increased in metastatic cancer of the mammary gland, in skin melanoma, and in ovarian cancer. The serum levels of ceruloplasmin increased 27, 20, and 44 percent, respectively, for those tumors, and the copper increased by 41, 35, and 51 percent respectively, for those same tumors as compared with normal tissue. Again there was no connection between the copper and the tumors as a causative agent.

Workers in Hong Kong (Fong, et al. 1977) have been investigating copper concentrations in cases of esophageal cancer in both humans and animals. They report that serum copper is increased slightly and that this is paralleled by a decrease in zinc content.

In summary, it must be stated that evidence for the oncological effects of copper, even at high concentrations, is essentially nonexistent. With the exception of the references cited, there appear to be no reports of copper as a causative agent in the development of cancer. There is much more evidence that a deficiency of copper will have adverse effects both in animals and in humans due to its essential role in the functioning of many enzyme systems.

CRITERION FORMULATION

Existing Guidelines and Standards

Far more attention has been given to the problems of copper deficiency than to the problems of excess copper in the environment. The 1 mg/l standard which has been established for copper levels in water for human consumption has been adopted more for organoleptic reasons rather than because of any evidence of toxic levels (Fed. Water Quality Admin. 1968).

The U.S. Occupational Safety and Health Administration has adopted standards for exposure to airborne copper at work. The time-weighted average for 8-hour daily exposure to copper dust is limited to 1 mg/m^3 of air. The standard for copper fume was changed in 1975 to 0.2 mg/m^3 (Gleason, 1968; Cohen, 1974).

There are no standards for copper in medical practice such as the treatment of burns or dialysis or for parenteral feeding.

Current Levels of Exposure

As has been mentioned earlier, principal concern has been for conditions of copper deficiency rather than copper toxicity. It has been suggested earlier that copper intakes in food and water may range from 6 to 8 mg per day, and that the percentage absorbed varies with the nutritional status. On the other hand, because of changes in food processing and, perhaps, because of better methods of analysis, copper intakes may not reach the 2 mg per day considered an adequate nutritional intake (Klevay, et al. 1977; Diem and Lentner, 1970; Robinson, et al. 1973; Schroeder, et al. 1966; World Health Organization, 1973; Cartwright and Wintrobe, 1964a).

The average concentration of copper in United States water systems is approximately 134 µg/l with a little over 1 percent of the samples taken exceeding the drinking water standard of 1 mg/l (McCabe, et al. 1970). When the U.S. Public Health Service studied urban water supply systems, they found that only 11 of 969 systems had copper concentrations greater than 1 mg/l (U.S. Dep. Health Educ. Welfare, Pub. Health Serv. 1970).

In 1966, the National Air Sampling Network found airborne copper concentrations ranging from 0.01 to 0.257 $\mu g/m^3$ in rural and in urban communities, respectively. Levels of copper as high as 1 to 2 $\mu g/m^3$ were found near copper smelters, but this was not considered hazardous (Natl. Air Pollut. Control Admin. 1968; Schroeder, 1970).

Special Groups at Risk

Increased copper exposure, with associated health effects, has occasionally occurred in young children subjected to unusually high concentrations of copper in soft or treated water that has been held in copper pipes or stored in copper vessels. Discarding the first water coming from the tap can reduce this hazard. Similar problems have developed in vending machines with copper-containing conduits where acid materials in contact with the copper for periods of time have dissolved copper into the vended liquids.

Other groups that may be at risk are medical patients suffering from Wilson's disease, and those patients who are being treated with copper-contaminated fluids in dialysis or by means of parenteral alimentation. These are medical instances in which the copper content of the materials used should be carefully controlled.

A final group that may be subject to risk of copper toxicity consists of those people occupationally exposed to copper, e.g., industrial or farm workers.

In reviewing the medical and biologic effects of environmental pollutants, the National Research Council Committee (Copper, 1977) pointed out that use of livers from animals fed high levels of copper in the diet could produce a baby food product that was excessively high in copper. The Committee also raised the question of exposure to copper from intrauterine contraceptive devices (IUDs), but subsequent reports have failed to demonstrate any abnormal accumulation of copper because of the use of these devices.

Basis and Derivation of Criterion

Copper is an essential dietary element for humans and animals. A level of 2 mg per day will maintain adults in balance (Adelstein, 1956) and has been considered adequate, although because of interactions with other dietary constituents which limit absorption and utilization, a requirement level must be considered in conjunction with such constituents as zinc, iron, fiber, and ascorbic acid. The minimum level meeting requirements for copper intake in intravenous feeding was 22 µg copper/kg body weight. (Vitter, et al. 1974).

The short biological half-life of copper and the homeostasis that exists in humans prevents copper from accumulating, even with dietary intakes considerably in excess of 2 mg per day. In the opinion of many investigators, there is much more likelihood of a copper deficiency occurring than of a toxicity developing with current dietary and environmental situations.

Although acute and chronic levels of intake may occur, there are no good data which define these levels. It has been suggested that chronic intakes of 15 mg of copper per day may produce observable effects, but if zinc and iron intakes are also increased, much higher levels may be consumed without adverse reactions. The data for acute toxicity are even more uncertain, since practically all human information stems from cases of attempted suicide.

The available literature leads to the conclusion that copper does not produce teratogenic, mutagenic, or carcinogenic effects. The limited information available indicates that where such action has occurred, e.g., with mixtures of copper sulfate and lime, arsenic, or enediols, the copper should be considered as interacting with the other materials and not as the active material.

The current drinking water standard of 1 mg/l is considered to be below any minimum hazard level, even for special groups at risk such as very young children, and therefore it is recommended that this level be maintained for water quality purposes.

Since the recommended criterion of 1.0 mg/l is based on organoleptic effects and is not a toxicological assessment, the consumption of fish and shellfish will not be considered as a route of exposure.

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